THE KIDNEY

Structure and Function in Health and Disease

To colleagues among
the anatomists, biochemists,
physiologists, pathologists, and physicians
who have made this volume possible

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FRONTIS. *Kodachrome* microphotographs of two afferent arter
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more
acido are frequently observable in these large cells in the mouse and cat, are rarely, if ever, observed in the dog and man.

The brush border of the proximal tubules is visible as a hazy band (Preparation of Dr. Irving Graef)

Frontispiece (See back of page for legend.)

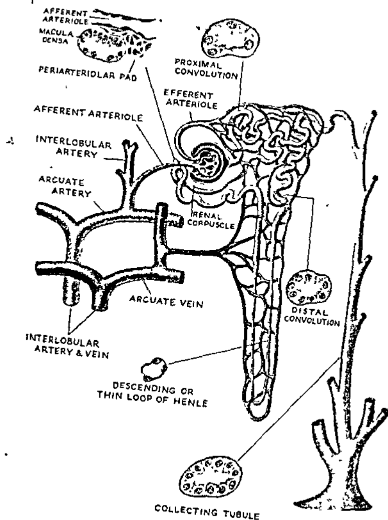


PLATE I. Diagram showing the essential features of a typical nephron in the human kidney.

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THE KIDNEY

Structure and Function in Health and Disease

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PREFACE

Many years ago Claude Bernard* (1878) pointed out that the higher animals 'have really two environments. a *milieu extérieur* in which the organism is situated, and a *milieu intérieur* in which the tissue elements live. The living organism does not really exist in the *milieu extérieur* (the atmosphere if it breathes, salt or fresh water if that is its element) but in the liquid *milieu intérieur* formed by the circulating organic liquid which surrounds and bathes all the tissue elements, this is the lymph or plasma. . . The *milieu intérieur* surrounding the organs, the tissues and their elements never varies; atmospheric changes cannot penetrate beyond it and it is therefore true to say that the physical conditions of environment are unchanging in a higher animal each one is surrounded by this invariable *milieu* which is, as it were, an atmosphere proper to itself in an ever-changing cosmic environment Here we have an organism which has enclosed itself in a kind of hothouse. The perpetual changes of external conditions cannot reach it, it is not subject to them, but is free and independent. . . All the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment.'

Though Bernard arrived at his view of the constancy of the internal environment from relatively few facts, investigations since his time have repeatedly confirmed and broadened the application of his principle. Cannon,[326] in his study of the autonomic nervous system, was led to extend Bernard's principle by recognizing that the con-

* The contributions of Claude Bernard (1813-78) to physiology were many and varied and entitle him to a place of high honor in the history of this science. Among his discoveries were the vasomotor nerves, glycogen and the nervous control of glycogen storage in the liver, carbon monoxide-hemoglobin, and the action of curare in blocking nerve impulses. His concept of the constancy of the internal environment was, however, perhaps his greatest contribution. Haldane has said, 'No more pregnant sentence was ever framed by a physiologist.'

stancy of the internal environment, which he designated as a homeostatic state, is in itself evidence that physiological agencies are acting, or ready to act, to maintain this constancy. These physiological agencies are themselves excited to action by some slight deviation of the homeostatic state. Thus in Cannon's view the compensation, direct or indirect, is itself automatically elicited by the environmental change. The term 'constancy' is, of course, used to signify 'limited variability.' Incidental or cyclical variations in the composition of the body fluids do occur, and in fact such variations play an important role as activating factors in the organism, but on the whole these variations are of a small order of magnitude because of the organism's regulatory powers.

The principles formulated by Bernard and Cannon are especially pertinent to the problem of renal function. In all the higher animals the plasma has indeed a remarkably constant composition, not only from individual to individual but among distantly related groups. This constancy is in large part a consequence of the activity of the kidneys, which under all conditions excrete a urine of such composition as to offset any tendency toward deviation in the composition of the plasma. In the last analysis, composition of the plasma is determined not by what the body ingests but by what the kidneys retain and what they excrete. It may fairly be said that this regulatory function, so long overlooked, is just as important as the excretion of the waste products of metabolism or of foreign substances, which hitherto has received nearly all the emphasis.

In the long view of the matter, the writer believes that regulatory and excretory operations receive about equal emphasis in this book, though it may seem at first glance that disproportionate emphasis is placed on some rather highly specialized problems. It may also seem that too little emphasis is placed on detailed renal pathology. But a writer so close to his subject admittedly cannot always see the woods for the trees, and it may be pleaded that there are good historical reasons for these aberrancies.

The study of tubular excretion began with phenol red and was carried on by means of other foreign substances (diodrast, p-aminohippuric acid) because of the analytic and methodologic limitations which then and still restrict the pursuit of quantitative renal physiol-

ogy. These studies led, however, to reliable methods for the measurement of the renal blood flow. There may be no such thing as a 'functional lesion' (as opposed to a visible one), but functional imbalance in the renal tubules can lead to serious disturbances of salt and water balance in Addison's disease or chronic congestive heart failure. Current methods of study of renal function may be too elaborate for general clinical application, but no method is to be disdained if it can aid significantly in deciding the issue between life and death. We can only hope that the information already gained has proved sufficiently useful to allay the concern, expressed by Addis,[14] Drury (in *Festschrift for Thomas Addis*),[545] and others, that renal physiologists have abandoned the sick in order to pursue complicated and specious theorems in ivory towers, or have overlooked the fact, so pertinently emphasized by Oliver (also in the *Festschrift for Thomas Addis*),[1582] that in this molecular world, structure always underlies function.

May 1950
New York

H. W. S.

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PART IV

THEORIES OF RENAL FUNCTION

It was first suggested by Ludwig in 1844 that urine formation begi with a passive process of filtration of a protein-free fluid in th glomeruli, effected by the hydrostatic pressure of the blood. Th supposition is strongly supported by the structure of the glomerulu itself. The membranes to be traversed (the endothelial capillary walls, the basement membrane, and the visceral layer of capsular epithelium) seem too thin and structureless for specific activity. In this view the filtrate, essentially identical in composition with the plasma except for the absence of protein, must undergo its final elaboration into urine during its passage down the tubules.

But when we consider the function of the tubules, this concept of filtration is no longer adequate. The tubule in its entire length is supplied by blood that, having been through the capillary tuft of the glomeruli, has lost a great part of its pressure and, therefore, the driving force necessary to effect filtration, especially against the osmotic pressure of the plasma proteins. Moreover, except in the thin limb of the loop of Henle, the cells of the tubule are high cuboidal cells of a nature that argues not only against filtration, but also against the easy diffusion of solutes. Their structure suggests that they are capable of carrying out complex chemical operations analogous to those performed by glandular cells in other organs, as well as of establishing and maintaining considerable differences in composition between the peritubular fluid and the tubular urine. Three major operations with respect to urine formation might be carried out by these tubule cells:

1. They might absorb substances from the glomerular filtrate and return them to the peritubular fluid (tubular reabsorption of glucose, etc.).

2. They might remove substances from the peritubular fluid and

discharge them into the tubular urine (tubular excretion * of phenol red, diodrast, etc.).

3. They might elaborate new substances that could be discharged into the tubular fluid (tubular secretion).

The problem, then, is this: to what extent does filtration, tubular reabsorption, tubular excretion, or chemical transformation enter into the conservation or excretion of any particular substance? The difficulties in answering this question are obvious, for even where we are certain that a substance is not synthesized by the kidney (i e. phenol red), all three processes, filtration, reabsorption, and tubular excretion, may possibly be involved, with the relative participation of each entirely unknown. It would be possible to erect an elaborate theory to explain the formation of urine in terms of filtration plus reabsorption, or filtration plus reabsorption plus tubular excretion, without being able to prove its validity at any point. And two investigators, viewing the same evidence, might disagree emphatically about the interpretation of the evidence. Such, in fact, was the history of theories of renal function until quite recent years.

Bowman (1832), in the classical paper in which he described the true relation of the glomerulus to the tubule, suggested on purely morphologic grounds that the former excreted only water and salts,

* The term 'secretion' was long used in renal physiology as synonymous with over-all excretion, but in recent years it has come into more restricted use to denote tubular excretion in particular, essentially as defined above In Cushny's day the word secretion still carried the implication of 'vital activity' In attempting to give a definition of secretion as it is currently used by non-vitalistic physiologists, perhaps it is best to describe it as the transportation of a substance from a low concentration to a high concentration, under such conditions that work must be performed In the case of the renal tubules, the energy for this work is supplied locally by the metabolism of the tubule cells. But, even so, no fundamental distinction is involved, for work must also be performed in glomerular filtration (in the form of increasing the osmotic concentration of the plasma proteins), only in this instance the energy is supplied by the metabolism of the heart and is transmitted to the kidney by the blood. Although we are still ignorant of how energy is made available or utilized in tubular excretion (such studies are just beginning), there is in our concept of it no implication of vitalism, and the term 'secretion,' stripped of its older ambiguity, may serve as a convenient synonym for it However, since it means nothing more than tubular excretion, we have preferred the latter expression, reserving 'secretion' for such local metabolic operations as the formation of ammonia

the other components of the urine (urea, uric acid, etc.) being excreted by the tubules. Two years later Ludwig advanced a more definite formulation which, as subsequently elaborated by himself and his students, consisted essentially of a simple physical or mechanical theory. He suggested that a protein-free filtrate was pressed out of the glomerular capillaries by the hydrostatic pressure of the blood, and that this fluid was subsequently concentrated in the tubules by the diffusion of water and various solutes. The activity of the tubules, he believed, could be explained simply in terms of the relative osmotic pressure and protein content of the tubular urine and peritubular blood.

In 1874 Heidenhain modified the original Bowman theory by positing that the glomeruli 'secreted' water and salts, this glomerular secretion being enriched with various additional salts, waste products, and foreign substances by the specific activity of the tubule cells. In Heidenhain's view the tubular epithelium was charged with the major responsibility of removing from the blood most of the solids that appear in the urine and a certain amount of the water as well, in accordance with the needs of the body at the moment. The protagonists of the Ludwig theory had performed numerous experiments indicating that the rate of urine formation paralleled the blood pressure, in rebuttal, Heidenhain asserted that it was not blood pressure but the rate of blood flow that was important; he adduced evidence that the tubules could at least excrete certain dyes quite independently of the glomeruli, and he argued that the filtration theory required an incredible quantity of filtrate to be formed to account for the known excretion of urea. For many years the two points of view remained irreconcilable. Ludwig's theory, although physiologically inadequate, had the advantage of physical simplicity, Heidenhain's theory, although physiologically adequate, demanded great discrimination on the part of the tubule cells and appeared to invoke some 'vital' force to propel water, waste products, etc., through the tubule cells and into the lumen. 'Vitalism' was fast being driven out of respiration, digestion, and other physiological phenomena, and the 'intelligence' of the tubule cells, implicit in Heidenhain's theory, seemed to give 'vital' forces a fresh lease. The choice of theory in this matter was influenced nearly as much by the individual investigator's bias on this philosophical question as by the experimental evidence.

During the next fifty years the respective natures of glomerular and tubular activity were debated back and forth, with no conclusive evidence to settle the argument. One opinion did come to be widely held: namely, that urine formation begins with the simple ultrafiltration of plasma in the glomeruli. But on the fate of this filtrate in the tubules and on the relative importance of tubular reabsorption and tubular excretion, there was little agreement, for the evidence seemed full of unintelligible contradictions.

When Cushny wrote his well-known monograph, *The Secretion of Urine*, in 1917, he stated in his prefatory letter to Starling:

> It is often complained that the physiology of the kidney given in textbooks is made up of a wrangle between the two great views of its activity. . . I have not avoided the controversy, but I have at any rate given the ascertained facts apart from the discussion, so that they at least may remain, whatever theory of kidney activity may survive. The different views are presented, and one is advocated which differs in some respects from any that has been accepted hitherto, and which embraces some of the features of each of its precursors. Since it has been developed gradually from the work of many, it would not be fair to attach to it the name of any one investigator, and I have therefore called it 'the modern view'; . . . If it serves as an advanced post from which others may issue against the remaining ramparts of vitalism, its purpose will be attained
>
> You will probably complain that instead of presenting the facts and following them to the theoretical principle to which they point, I have just stated the theory and then discussed how far each set of observations can be brought into accord with it . . The facts are so multitudinous that unless the student were first given some general scheme on which he could arrange them, he would be lost in detail and might fail to appreciate where the path was leading.

When the second edition of Cushny's monograph appeared in 1926 the issue of 'vitalism' was dead, but the 'wrangle' concerning the role of tubular excretion was not. The processes that had once savored so strongly of 'vital' activity were still warmly defended on quite mechanistic grounds by many investigators. But in the interim Cushny's 'modern theory' had accomplished the chief thing the author had desired for it: it had served to guide investigators so that they could ask intelligent questions about the kidney and hope for intelligible answers, which is, of course, the chief function of any theory.

A brief review of Cushny's theory will serve to introduce the student to the more recent investigations in this field. Cushny supposed, as had Ludwig in 1844, that the initial step in urine formation is the separation in the glomerulus of a fluid essentially identical in composition with plasma except for the absence of the plasma proteins, to which the capillaries of the glomerular tuft were presumed to be impermeable. This capsular fluid is formed at the expense of the hydrostatic pressure of the blood, and hence the source of energy for its formation is ultimately the heart. The chief endothermic reaction issues from the fact that the plasma proteins must be concentrated osmotically when protein-free capsular fluid is separated from the plasma. The capsular fluid is supposed to contain all the filterable constituents of the plasma (sodium, potassium, chloride, sulphate, urea, amino acids, glucose, etc.), in the same concentration per unit volume of water * as these are present in the plasma, except for such inequalities in the distribution of ions as might arise from the presence of non-filterable proteins (Donnan effect). Just which molecules pass into the filtrate and which do not must remain a matter of speculation until the porosity or permeability of the glomerular tuft is actually measured. But that the great majority of plasma solutes pass through the glomerulus must be accepted on the grounds that, if they did not, the total osmotic pressure, by tending to draw water back into the capillaries from the capsular space, would oppose and effectively prevent the process of filtration itself.

It follows in principle that such substances as are present in the plasma but absent from the urine must be reabsorbed by the tubules as the glomerular filtrate passes along them on its way to the bladder. It must also be supposed that a large part of the water present in the filtrate is also reabsorbed by the tubules, since certain waste products, such as creatinine, urea, etc., may be present in the urine in many times the concentration that they are present in the plasma and therefore in the capsular fluid. Cushny, denying the role of tubular excretion, supposed that this increased concentration is effected only by the reabsorption of water. In view of the fact that different substances are concentrated to a different extent, it was supposed that

* The solutes in the filtrate would be more concentrated per unit volume of solution, in consequence of the abstraction of the plasma proteins, which occupy from 5 to 7 per cent of the plasma volume.

some or all of these substances are reabsorbed by the tubules in varying degrees. Substances which need to be conserved by the organism, such as sugar, amino acids, chloride, etc., are perhaps reabsorbed completely or nearly so, while some waste products, such as creatinine, are possibly not reabsorbed at all. Cushny believed that substances in the first group are completely reabsorbed so long as the plasma concentration is below a certain critical or threshold level, and therefore he called these 'threshold' substances, a term first used by Bernard *in describing the excretion of glucose.* Waste products, such as creatinine, are rejected by the tubules independently of their plasma level, and these he called 'no-threshold' substances.

At first sight, the process whereby water and the many threshold substances that pass into the glomerular filtrate are reabsorbed appears to be extraordinarily complex, but Cushny attempted to resolve this complexity by a simplifying assumption, namely, that what is *actually reabsorbed by the tubules is a fluid of constant composition,* a perfected 'Locke's solution' or protein-free plasma. The tubule cells are so constructed, he supposed, that they draw from the glomerular filtrate optimal quantities of a fluid having an optimal composition and return this fluid to the plasma, thus maintaining the optimal composition of the latter. Everything left behind in the tubular urine after the removal of this optimal fluid passes into the collecting ducts as the final urine. 'The formation of the glomerular filtrate is due to a blind physical force, the absorption in the tubules is equally independent of any discrimination, for the fluid absorbed is always the same, whatever the needs of the organism at the moment.'

It is open to question whether or not the hypothesis of the reabsorption of a fluid of optimal composition is really a simplification. In order that the tubules may reabsorb a fluid of optimal composition containing a large number of chemical substances in different concentrations, there would seemingly be required just as elaborate a physical-chemical apparatus as there would for the tubules to reabsorb each of these constituents separately and independently. And a preferential choice between tubular reabsorption and tubular excretion of particular chemical entities can scarcely be based on physical-chemical grounds, for this would appear to be merely a matter of the physiological orientation of the cell. So the advantage of this part of

Cushny's theory is slight. In principle, however, the theory as a whole was very attractive to most investigators because it treated the kidney as an organ of fixed and predictable function, like muscle and nerve. But where this forthright, mechanistic interpretation was the strength of the theory, its weakness lay in oversimplification, which was achieved by the *a priori* exclusion of tubular excretion. True, there was no incontrovertible proof of the existence of this process; but neither was there any incontrovertible proof of the existence of either filtration or reabsorption. Every fact known about the kidney could have been explained in at least two ways. The exclusion of tubular excretion was based in no small measure on the belief that such a process must readmit 'vitalism,' with its uncontrolled and inexplicable forces, into the domain of renal physiology. In retrospect we see that this fear was quite unjustified. Tubular excretion, viewed as a consequence of the physical-chemical organization of the tubule cells, can be looked upon as being as mechanistic as filtration itself. In fact, in the absence of any knowledge how the tubules could reabsorb the 'optimal' fluid, Cushny was forced to ascribe this process to 'vital activity,' even though this activity was reduced to attractively constant and definable proportions.

So, while physiologists were generally prepared to accept glomerular filtration and tubular reabsorption, at least in principle, they remained divided on the issue of tubular excretion. The 'wrangle' of disagreement, which Cushny had justly deplored, was little abated until recent years, when Richards and his collaborators demonstrated beyond question the existence of glomerular filtration and tubular reabsorption, and Marshall and his collaborators demonstrated the existence of tubular excretion, thus showing that both schools were right. Our current knowledge of renal physiology demonstrates that, though glomerular filtration plays an important part in urine formation, this process is supplemented by tubular excretion as well as tubular reabsorption in all animals, including man. Cushny's idea of the reabsorption of an 'ideal fluid' of constant composition has been confounded by the discovery that the reabsorption of water, glucose, sodium, phosphate, amino acids, vitamins, and many other substances are more or less independent processes, in many cases possessing specific quantitative limitations, and that in addition considerable quantities of waste products, such as urea, uric acid, and sulphate,

are normally reabsorbed as well. Thus the simplification Cushny strove to achieve by the reabsorption of an ideal fluid has momentarily been lost.

It is not inappropriate to point to the history of renal physiology as typical of the history of science, and particularly of the history of medicine. It has been a history of rival theories, each based upon inconclusive evidence. Its errors have been compounded by over-simplification in the matter of theory and underexamination in the matter of critical investigation. Renal physiology has now passed into a quantitative phase where unsupported speculation and empirical description are no longer warranted.

Part I



NOTE

The following symbols are frequently used throughout this book:

C = plasma clearance (UV/P) of any substance, the nature of which is indicated by an appropriate suffix, viz: C_{IN}, C_{CR}, etc.

C_F = filtration rate (or clearance), whether measured with inulin or (in the dog) with creatinine or any other suitable substance.

Since all clearances are expressed in cc/min., the time unit has generally been omitted.

T = rate of tubular transport, whether reabsorptive or excretory;

Tm = maximal rate of tubular transport under conditions of saturation; in both instances the nature of the substrate is indicated by an appropriate suffix, viz: T_G, Tm_G, T_D, Tm_D, etc.

FF = filtration fraction (uncorrected for E), i.e. C_{IN}/C_D or C_{IN}/C_{PAH}

E = extraction ratio.

Where the *total* renal plasma flow or renal blood flow is calculated by dividing C_D or C_{PAH} by the extraction ratio, it has been designated as such in order to avoid confusion with uncorrected clearances. The filtration fraction when so corrected is called the true *filtration fraction.*

Surface area. Since all clearances in man are conventionally corrected to the arbitrary value of 1.73 sq m., this correction is not generally stated in the text.

CHAPTER I

Anatomy

The complex function of the kidney in man and other vertebrates would suggest that this organ has an extraordinarily complex structure. On close examination, however, it is found to be made up of a very large number of structurally similar and anatomically simple functional units. Each of these units, or nephrons, consists of a glomerulus attached to an unbranched tubule, the latter being differentiated into three anatomically distinct portions. In each human kidney there are about one million nephrons, which drain by way of a series of collecting ducts into the renal pelvis and thence by the ureter into the bladder. The essential features of a typical nephron in the human kidney are illustrated in plates I and II

GLOMERULI

The formation of urine begins in the *glomerulus* (Malpighian body), which consists of an elaborate and almost spherical tuft of capillaries supplied with blood through a short, wide *afferent* arteriole. This capillary tuft is formed by the abrupt division of the afferent arteriole into 2 or 4, rarely up to 10, primary branches, which in turn subdivide again, at times into as many as 50 capillary loops, each loop having a length 2 or 3 times the diameter of the whole tuft The primary branching of the capillaries near the arteriole

tends to give the tuft a lobulated structure. There are no shunts within the glomerulus and the capillaries do not anastomose with each other [2228] but coalesce into an *efferent* arteriole, which in turn breaks up again into a second capillary system (*peritubular capillaries*) around the tubules.

The relation between glomerulus and tubule can be expressed by saying that the capillary tuft is thrust into the expanded but closed end of the tubule in such a manner that this tuft becomes enveloped in a spherical double-walled capsule (*Bowman's capsule*) derived from the tubule itself, the inner or *visceral* layer of the capsule being closely applied to the capillary tuft, the outer or *parietal* layer being expanded into an enveloping thin-walled sphere. The space generated between the visceral and parietal layers of the capsule (*capsular space*) remains in direct communication with the lumen of the attached tubule. The arrangement is such that any fluid passing through the capillaries and the visceral layer of the capsule is collected in the capsular space and thence drains down the tubule. In man and the dog both the visceral and parietal layers of the capsule are composed of low or squamous epithelium, but in mice and some other mammals both layers, and particularly the parietal layer, may consist of cuboidal cells similar in structure to those of the proximal tubule.[444] In rare instances, the proximal tubule may extend as an irregular protrusion into Bowman's capsule.[1420]

In microscopic section, the glomerular capillary loops appear as a tangled skein of vessels of inconstant caliber, and the separate membranous layers can be fully distinguished only by refined histological techniques. The visceral layer of the capsule is primarily composed of an optically structureless basement membrane, continuous with the basement membrane of the tubule, and a very thin reticulum of epithelium, which is continuous with the tubular epithelium. This visceral membrane is attached to the arterioles at the root of the glomerular tuft; at some points it is closely applied to individual capillaries, while at others it envelops capillary loops that have no basement membrane of their own. The intercapillary or 'axial' space contains an infrequent third type of cell (neither endothelial nor epithelial), possibly a connective-tissue cell, designated by Zimmerman as the

mesangium. There is still some doubt about the fate of these cell types in glomerular disease. In acute glomerulonephritis, both the capillary and mesangial cells suffer inflammatory changes with proliferation and fibrosis, the axial space being invaded by polymorphonuclear leukocytes. In eclampsia, apparently only the mesangial cells are involved, suffering marked swelling and vacuolation, which give the glomerulus a reticulated appearance. In intercapillary glomerulosclerosis, glycoprotein accumulates in the axial space, and lipoid accumulates here in lipoid nephrosis.[1345]

The three primary membranes of the glomerulus—capillary endothelium, basement membrane, and capsular epithelium—are usually considered continuous, in the sense of having no openings or defects. However, some anatomists contend that the visceral epithelium is discontinuous, and that the individual epithelial cells are highly irregular in shape and exhibit delicate discrete processes, which invest the glomerular capillaries in the manner of the pericytes that are applied to capillaries elsewhere in the body.[118, 1320] If such is the case, the glomerulus may be said to be composed of a tuft of capillaries supported only by an extremely thin, almost invisible basement membrane.

The organization of the nephron is best understood in the light of embryological development. The capillary tuft and the renal tubule develop out of different anlagen and for a time grow independently in the embryonic kidney. When the tuft and tubule first make connection, the latter is a short S-shaped tube, closed at both ends. This short tubule grows by extension in length and one end ultimately establishes connection with an outgrowth of a collecting duct, while the other end expands and, by invagination, develops a concavity on one side into which the capillary tuft grows, this tuft ultimately becoming completely enfolded within the invaginating tubule wall to form Bowman's capsule.

TUBULES

In the adult mammalian kidney, or metanephros, each tubule,* after extensive convolutions near the glomerulus (*proximal convoluted tubule*), descends in a more or less straight path to a

* The structure of the mesonephric nephron, which lacks a thin segment, is briefly reviewed by Huber.[1344]

capsular space. Here this membrane is normally so thin th
discernible only with special stains, but there is evidenc
proliferation and thickening may play an important r
certain types of glomerular disease.

COLLECTING TUBULES

The *collecting tubules* consist of epithelium that is quite dif
from the other parts of the nephron, a distinction in ke
with its separate embryological origin. The cells vary in h
in different portions of the collecting system but are a
universally arranged in a single smooth layer with dark-sta
spherical nuclei all in the same relative position. The cytolo
the collecting tubules does not suggest any specialized fur
other than service as conduits, and they are so treated by r
all writers. There is some evidence, however, that may be
preted as indicating that they have a reabsorptive function
ticularly for water.

DETAILED VASCULATURE OF THE MAMMALIAN KIDNEY

After the renal artery enters the hilus of the kidney it di
into two sets of end-arteries, a *ventral* and a *dorsal* set, v
progressively subdivide into three further orders, the *inter*
and/or *arcuate* and *interlobular* arteries. Numerous short ar
twigs, the *afferent arterioles*, each of which directly suppl
glomerulus, are given off from the interlobular arteries.
muscle fibers in the interlobular artery and the afferent arte
are arranged in the spiral bundles of a helix.[1150] From the glo
ular capillaries the blood is carried off by the *efferent arte*
which has a somewhat variable structure ranging from an e
thelial vessel provided with a network of cells resembling Ro
cells to a typical arteriole invested by smooth-muscle cells.[11]
efferent arteriole breaks up into a second network of capilla
the distribution of which varies with the level of the glomer
in the cortex: in the inner third of the cortex (juxtamedu
glomeruli) the efferent blood is directed in a stra[illegible] co
to the medulla, whereas in the
blood is distributed to the a[illegible]
(plate II).

In both the cortex and the medulla the peritubular capillaries converge into veins whose distribution follows more or less the local tubular pattern; in the cortex the confluent veins have a stellate arrangement, while in the medulla their course is straight, paralleling the tubules. The interlobular veins converge into the arcuate veins paralleling the arcuate arteries, and these finally ...oin to form the renal vein, which emerges, in the hilus of the ...dney, adjacent to the renal artery.

JUXTAMEDULLARY CIRCULATION

...re are notable differences in the postglomerular circulation in the ...r two-thirds or so of the cortex and the inner third adjacent to ...medulla (plate 11). The glomeruli in the inner portion of the cortex ...been called the juxtamedullary glomeruli by Heggie[915] to dis...sh them from the cortical glomeruli. ...Peter[1886] first demonstrated, the loop of Henle of those tubules ...from the cortical glomeruli passes only a relatively short distance ...e medulla, the thin segment of this loop being very short On the ...hand, the loop of Henle of the tubules of the juxtamedullary glomeruli descends deeply into the medulla, often as far as the papilla, the greater part of the loop within the medulla being made up by the thin segment.

Trueta, Barclay, Daniel, Franklin, and Prichard[2033] have recently contributed substantially to our knowledge of the finer circulation in the juxtamedullary region by detailed studies of injected kidneys in several mammals (rabbit, cat, guinea pig, rat, dog, and man)

The efferent arterioles of the cortical glomeruli are much smaller than the afferent arterioles, whereas in the juxtamedullary glomeruli the ef...ferent arterioles are nearly as large as the afferents, a difference hitherto ...recognized and interpreted as related to the fact that the juxtamedullary glomeruli must supply nearly all the blood to the medulla by way of the *vasa recta*. Typical juxtamedullary glomeruli are situated only in the ...ner third of the cortex and are supplied by afferent arterioles arising ...most instances from the proximal portions of the interlobular arteries, ...ough occasionally directly from an arcuate artery, while cortical ...meruli occur in all zones of the cortex peripheral to the juxtamedullary ...on, only a few occurring in this deepest zone

...he efferent arteriole of the typical cortical glomerulus breaks into ...llaries of small caliber, which descend with and are distributed ...d the thick descending and ascending limbs of the loop of Henle,

they may easily be ruptured by an increase in pelvic pressure, a circumstance that may explain the phenomenon of pyelovenous backflow sometimes observed after the use of excessive pressure in retrograde pyelography (ch. XXVI).

ARTERIOVENOUS ANASTOMOSES AND DIRECT ARTERIAL SUPPLY TO THE MEDULLA

Bowman (1832), in his classic description of the circulation of the mammalian kidney, said that all the blood reaching the tubules traverses the glomeruli and is distributed from the efferent glomerular arterioles. Bowman's description was based only on the fact that this seemed to be the fundamental pattern, and he had no occasion to argue the question of possible exceptions. However, within a few years Ludwig (1847–8) challenged Bowman's description by asserting that some interlobular arteries in the outer cortex terminate directly in the peritubular capillary plexus without the interposition of a glomerulus. Of greater interest, however, are potential sources of aglomerular blood within the renal vasculature proper. In 1857 the American anatomist Isaacs [185] pointed out that in some cases an afferent glomerular arteriole may give off a twig which communicates directly with the peritubular capillary plexus. It was some years later (1871) before Ludwig described this branching of the afferent arteriole,* and such branches may appropriately be called Isaacs-Ludwig arterioles. A third alleged form of non-glomerular circulation is represented by arterioles that arise from either the subcortical or interlobular arteries to descend directly into the medulla, called *arteriolae rectae verae* in contradistinction to the descending efferent arterioles, called *arteriolae rectae spuriae* or *vasa recta*.

Numerous anatomists have confirmed the existence of all three types of non-glomerular arterioles [1929] but claimed that non-glomerular arterioles of any type are so rare as to be considered only anomalies, though they may increase in number and functional importance with advancing age. It is clearly established by the studies of Huber,[1047] McCallum,[1287] Oliver,[1549] MacNider,[1355]

* Bieter observes that the remarks of Schweigger-Seidel make it clear that this circulatory arrangement had been observed by Ludwig and his pupil Gerlach, and by Virchow and others at a date considerably before Ludwig's article in Stricker's *Handbuch* was written

and others [1270, 1880] that in pathological kidneys and in kidneys from patients of advanced age, many degenerate glomeruli may be seen in which the capillary tuft has virtually disappeared; the afferent and efferent arterioles form a continuous trunk through the vestige of the glomerulus and are united by a single dilated glomerular capillary. The remaining capillaries, if present at all, form mere appendages springing from one side of this trunk.

Aglomerular vessels formed by glomerular degeneration are thought by Trueta and his colleagues to be identical with the *arteriolae rectae verae* of other investigators, and the authors believe that similar degenerative changes lead to the formation of arterioles of the Isaacs-Ludwig type from typical cortical glomeruli, in which case the efferent vessel of the degenerate glomerulus joins the cortical-intertubular capillary network instead of the *vasa recta*. Such degenerative glomeruli have been found in the kidneys of all species; they occur most frequently in the juxtamedullary zone, and, since the degenerative glomeruli lack a capillary bed, the authors suggest that they afford virtual arteriovenous 'shunts' operating through the *vasa recta* system. Since the frequency of such degenerative glomeruli varies with age and disease in any one species, and since the actual number is small in comparison with glomeruli of normal capillary structure even in the juxtamedullary zone, their functional significance remains problematic.

Spanner,[1965] from injections of a single human kidney, believed that arteriovenous anastomoses occur with relatively high frequency in the sinus, cortex, and capsule, but this belief was not confirmed in the dog kidney by Shonyo and Mann [1880] or in other species by Trueta *et al.* The latter investigators found that, in the renal sinus, the interlobular arteries adjacent to the external walls of the calyces frequently carry small, highly coiled arterial twigs, which end either in the interlobular artery of origin or in an adjacent artery, but never in the venous system. Because of the great tortuosity of these peculiar arterial by-passes, these investigators call them *'coiled arterial vessels,'* and they suggest that it was such vessels Spanner mistook for arteriovenous anastomoses. They see no evidence of direct communications between the interlobular arteries and veins in the cortex of the normal kidney, and,

although venous vessels in the capsule anastomose freely with each other and with the veins of the perinephric tissues, arteriovenous anastomoses, if they exist here at all, are rare. Trueta and his colleagues reaffirm that, in the normal kidney, all the renal blood passes through the glomeruli (cortical or juxtamedullary), and that the medulla receives no blood other than what reaches it through the juxtamedullary glomeruli.

Barrie, Klebanoff, and Cates,[98] however, reaffirm an early observation by Golubew, that in the cortico-medullary junction certain tightly coiled arterioles derived from the arcuate arteries make direct communication with adjacent veins through one or more sinusoids, thus creating a virtual arteriovenous anastomosis. After leaving the sinusoid, the arteriole breaks up into a leash of vessels that supply the peripheral part of the medulla, thus affording a direct arterial supply to the latter. From this brief report it is not clear what relation these vessels have to the degenerate, canalized glomeruli described by previous investigators, or why a true arteriovenous anastomosis should communicate through a sinusoid bounded by a single layer of endothelium.

The two important points in all discussion of arteriovenous anastomoses in the renal circulation are their origin and their number. Since each kidney contains nearly 1,000,000 true glomerular vessels, it is not surprising that there should be a few anomalous vessels, particularly as a result of degenerative changes. Simkin, Bergman, Silver, and Prinzmetal [1896] have injected glass spheres into the renal artery of living rabbits and recovered spheres measuring 50 to 180 μ in diameter from the venous circulation. Spheres of even greater size (90 to 440 μ in diameter) were recovered from the renal vein of human kidneys perfused post mortem. Since spheres of this size can hardly pass through the capillary bed, the authors consider this indubitable evidence that renal arteriovenous anastomoses are present and functional in the living animal. The data are, however, not quantitative and might be explained by a relatively few anastomoses, having little or no functional significance. Clearance data and extraction ratios demonstrate unequivocally that not more than 8 per cent of the total renal blood flow normally passes directly from the arterial to the venous system in the human kidney (ch. xxv), this figure

including not only arteriovenous anastomoses but the blood which exclusively perfuses the renal capsule and the perirenal fat and such non-excretory tissues as the renal pelvis and major collecting ducts. In only a single circumstance (the rapid administration of concentrated serum albumin) is there evidence that any substantial quantity of blood may pass through the human kidney *without being cleared*, and the evidence is not yet firm that this phenomenon is a result of arteriovenous or transmedullary shunting.

In addition to the atypical arterioles described above, the fibrous and fatty capsules of the cortex possess a substantial arterial supply derived from the interlobular arteries, from the capsular artery itself, and irregularly from extrarenal sources such as the spermatic, lumbar, suprarenal, and phrenic arteries. There is, however, no information on the quantitative importance of these cortical-capsular connections.

LYMPHATIC VESSELS AND CONNECTIVE TISSUE

There is an elaborate network of *lymphatic vessels* in the cortex but apparently none in the medulla Larger lymphatic channels accompany the interlobar, arcuate, and interlobular vessels, surrounding them in an irregular anastomotic network, particularly rich around the arteries. A second plexus underlies the capsule, and a third penetrates the perinephric fat, the last two communicating freely with each other. In no case do the lymphatics within the kidney enter the glomeruli; all drain into renal lymphatic vessels which leave the kidney at the hilus and end in the lateral aortic nodes. The perinephric plexus drains directly into the upper lateral aortic nodes.

Valves are lacking in the renal parenchyma, but are present in the large trunks of the renal sinus.[1614]

The quantity of *connective tissue* in the normal mammalian kidney is small. Its branching and anastomosing fibers form diffuse networks everywhere in the narrow spaces between the tubules, the fibers being especially numerous and thick in the pyramids. A few strands of connective tissue enter the glomerulus along the blood vessels. Proliferation of this connective tissue throughout the kidney may play an important part in disease.

INNERVATION

The kidney receives a rich supply of sympathetic vasoconstrictor nerves, said to be second in bulk only to the adrenal gland. These nerves arise from the IVth dorsal to the IVth lumbar segments, although the functionally most important segments in the dog appear to be the last four dorsal segments. A combination of these fibers passing through the splanchnic and abdominal ganglia makes up the renal plexus, a network running along the renal artery from the aortic plexus to the renal hilum, from which fibers enter the kidney with the renal vessels and terminate among the afferent and efferent arterioles. Nerve fibers penetrate the basement membrane to end adjacent to the tubular cells, especially in the proximal segment, and others terminate among the juxtaglomerular cells, in the parietal layer of Bowman's capsule, and in the perivascular spaces of the glomerular tuft. Whether such fibers are afferent or efferent is undetermined.

Some of the preganglionic sympathetic fibers undergo synaptic junction in the lateral ganglia, others in the collateral ganglia, and still others in the kidney itself. Neither sympathetic vasodilators nor vagal fibers to the kidney have been demonstrated. Afferent fibers, at least from the renal pelvis and ureters and possibly from the renal parenchyma, play an important role in renal pain and in some types of anuria involving reflex vasoconstriction.[224, 879 918, 1929]

RENAL-PORTAL SYSTEM

All Vertebrata during embryonic life (pronephros and mesonephros) and all adult vertebrates (mesonephros) other than the Mammalia (metanephros) possess a *renal-portal system*· the veins draining the posterior part of the body (caudal, iliac, ovarian, spermatic, etc.) give rise to a pair of afferent renal veins (*vv portae renalis*, or renal-portal veins) which, before joining with the efferent renal veins, give off numerous radicles on either side, in some forms the free movement of blood from the renal-portal veins into the vena cava is obstructed by a membranous valve that possesses only a fine communicating channel, and consequently venous blood from the renal-portal veins is diverted through these radicles to reach the peritubular capillaries, from which it is ultimately collected into the efferent renal veins.[2118] The renal tubules of the meso-

nephros thus have a double supply of blood, the first from the efferent glomerular arterioles and a second from the renal-portal system. In some Amphibia, Reptilia, and Aves, shunts may connect the renal-portal veins with the efferent renal veins, making it possible for the blood from the former to by-pass the kidneys Similar shunts between the renal-portal veins and the posterior mesenteric veins occur in some Osteichthyes, Reptilia, and Aves, permitting blood to flow from the renal-portal to the hepatic portal system. Although the functional significance of the renal-portal system with respect to the adult kidney in submammalian forms has been challenged, the evidence shows that it does in fact deliver venous blood to the renal tubules without passage through glomeruli As Mossman[1481] remarks, phylogenetically the renal-portal system is one of the most fundamental features of the circulation in the vertebrates Indeed, it is the principal distinguishing characteristic between the mesonephros, which is the definitive kidney below the Mammalia, and the metanephros of the Mammalia. Indubitable evidence of function is available in the aglomerular fishes, of which some twelve or more families are known[1404] In those that have been well studied, the *only* blood supply to the kidney is venous in nature and is derived in large part from those venous channels that in other forms contribute to the renal-portal system (caudal vein, posterior cardinal vein, accessory caudal vein)[1402] The preponderance of tubular excretion over glomerular filtration in the glomerular fishes, frog, and chicken is also evidence in this direction (ch xvii).

In the Mammalia, as the mesonephros is replaced by the metanephros during embryonic development, the renal-portal system disappears, leaving only the pampiniform plexus as a remnant, and all blood to the kidney enters via the renal artery. (A trivial exception is presented by minor arterial connections between the renal capsule and the vasculature of perinephric organs) It seems fair to say that the mesonephros is primarily a tubular kidney in which the glomerulus is adjunctival; this [illegible]

malia, emphasis was again placed on glomerular function, and the renal-portal system was discarded

For many interesting details on renal architecture, tubule length, etc, in relation to habitat among the mammals, the reader is referred to Sperber's monograph.[1969] The older literature on gross and microscopic anatomy of the kidney and on renal function is summarized by von Möllendorf[2113,2114] and Ellinger[596]

CHAPTER II

Studies on Individual Nephrons

COMPOSITION OF THE GLOMERULAR FILTRATE

That the first step in the formation of urine consists of simple ultrafiltration in the glomeruli was first clearly demonstrated by Richards and his collaborators by actual analysis of the capsular fluid in the frog (*Rana pipiens*) and mud puppy (*Necturus maculosus*). In a brilliant and painstaking series of studies beginning in 1924 and extending over many years, these investigators applied the Chambers microdissection technique to the puncture not only of Bowman's capsule but also of various segments of the renal tubule of living animals. Developing microanalytical methods adapted to the small quantities of fluid thus obtained (0.5 cu. mm. or less), they successfully followed the changes in *composition of the urine as it passed from Bowman's capsule to* the bladder.[1706, 1707, 1708, 1710, 1718]

Glomerular puncture was first applied by Wearn and Richards[2163] to demonstrate that the glomerular fluid normally contains at best only traces of protein, thus substantiating a central point of the filtration theory. It was also shown that the capsular fluid contains glucose and chloride when the bladder urine is free of these substances, thus proving the actuality of tubular reabsorption of these substances.

Subsequent investigations have shown that, in both the frog and *Necturus*, the *osmotic pressure* of the capsular fluid and blood plasma is the same, as is also the *electrical conductivity*.[107,2125] The chloride content of the capsular urine * in both species is on the average a little higher than that of plasma; although the difference is within the error of the method it may be a real one explicable by the Donnan equilibrium.† [693,2164,2176] *Urea*,[2132] *glucose*,[2135] *inorganic phosphate*,[2124] *creatinine*,[217] and *uric acid*[214] (the last also studied in the snake) are present in the capsular fluid in the frog *in the same concentration as in plasma, and this is true of sodium* in *Necturus*[217] The capsular fluid also has the same pH as the plasma.[1468,1617] Glomerular filtrate forms in a single capsule at such a rate that, when the total number of glomeruli in the two kidneys is taken into account, the calculated quantity of water filtered is well above the maximal rate of urine excretion. ‡ In certain details these results have been confirmed by White and Schmitt[2210] and Ekehorn.[693]

Nearly all investigators have agreed that the blood pressure in the glomerular capillaries is adequate to effect a limited amount of filtration against the colloid osmotic pressure of the plasma. In man the mean arterial pressure may be taken as 90 mm. Hg and the average osmotic pressure of the plasma proteins as 24 mm.; in the frog and *Necturus* these figures may be taken as 29 mm. and 7.7 mm , respectively.[162,935,1204,2186] Assuming that the blood pressure is reduced by one-third to one-half in the glomeruli of both animals, a considerably higher filtration pressure would be expected in the warm-blooded forms, and therefore a greater volume of filtrate relative to each unit volume of plasma. Actually, *it has been established by clearance methods that an average of*

* In all these experiments, a protein-free fluid (capsular or tubular urine) is being compared with plasma, which contains considerable protein. Consequently an appropriate correction has been made in order to express plasma concentrations on the basis of mg/100 cc. of plasma water. No correction is indicated in the case of osmotic pressure

† The Donnan equilibrium is discussed in chapter XI.

‡ Although this calculation indicates that glomerular filtration can account for all the water excreted, similar calculations must be applied with caution to the excretion of other substances where a range not of several hundred per cent but of 25 or 50 per cent is critical in answering the question whether or not glomerular filtration is the sole process involved in their excretion

19 per cent of the plasma water is filtered in man [1939] and 12 to 15 per cent in the bullfrog.[677]

COMPOSITION OF THE TUBULAR URINE

The methods developed for the collection and analysis of glomerular fluid have been applied by Richards and Walker [1719] and their coworkers to the study of the tubular fluid in frogs and *Necturi*, and by Walker, Bott, Oliver, and MacDowell [2131] to similar studies in the rat, guinea pig, and opossum. Tubules have been punctured at various levels and fluid removed for analysis, or fluid of known composition has been perfused through a tubule by two micropipettes, the lumen of the tubule being closed on either side by the injection of a globule of mercury or mineral oil.

Since no fluid can be collected from a tubule when the glomerulus is cut off by compression, it is assumed that no water is excreted by the tubule. The extent of the reabsorption of water cannot be determined directly, and it is therefore uncertain whether a change in the concentration of a particular substance, as the urine passes down the tubule, is caused by subtraction of water or by the addition of the substance itself.

The data in figure 1 [2136] show that there is essentially no change in the osmotic pressure of the tubular urine during its passage along the proximal tubule; the typically hypotonic urine is formed in the distal tubule. Under the assumption that there is no tubular excretion of water, the progressive loss in osmotic pressure observed in the distal tubule must be a result of the reabsorption of osmotically active constituents, the chief of which is sodium chloride.

Final reabsorption of sodium (and chloride), and perhaps of other inorganic constituents, occurs in the distal tubule. Evidence is given below that as much as 30 per cent of the water of the glomerular filtrate is reabsorbed proximally; were not sodium chloride also reabsorbed in the proximal tubule, the chloride urine/plasma (U/P) ratio should be $1/(1.0 - 0.3)$ or 1.4, but this ratio rises only to about 1.1; hence some sodium reabsorption must occur in the proximal tubule as well. The disparity between the facts that the osmotic U/P ratio = 1.0 and the chloride U/P ratio = 1.1 can perhaps be explained by the preferential

proximal reabsorption of bicarbonate and possibly other anions.

That glucose reabsorption occurs in the proximal tubule of *Necturus* was first shown by White and Schmitt.[illegible] Data from the more extensive experiments of Walker and Hudson [illegible] confirming this are given in figure 2. The concentration of glucose

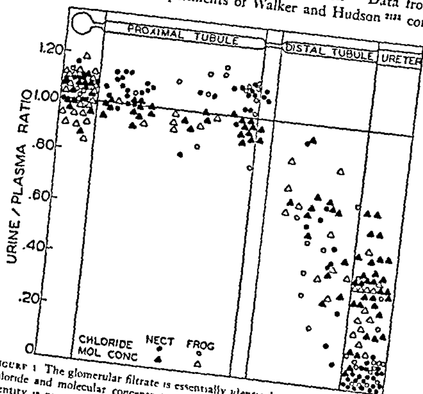


FIGURE 1 The glomerular filtrate is essentially identical with plasma, so far as chloride and molecular concentration (osmotic pressure) are concerned. This identity is preserved throughout the length of the proximal tubule, the reabsorption of chloride (and sodium) occurring in the distal tubule. (Walker, Hudson, Findley, and Richards [illegible])

iminishes rapidly as the filtrate moves down the proximal ubule, and when this has been half traversed, the concentration ay be as low as it is in the ureteral urine. However, the capacity reabsorb glucose is not limited to the first half of the proximal bule, for, when Ringer's solution containing glucose is slowly rfused through the distal half, the sugar is also reabsorbed.

the contrary, when a glucose solution is perfused through the distal tubule, its concentration remains the same or increases owing to the reabsorption of water. The sole site of the selective reabsorption of glucose is therefore the proximal tubule. In the

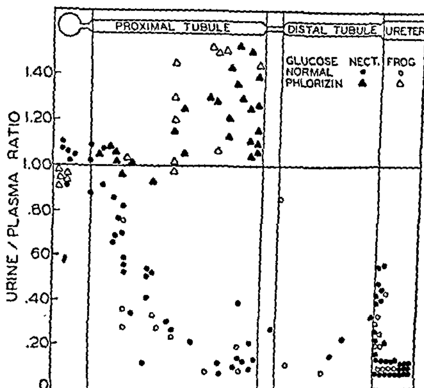


FIGURE 2. The glucose of the glomerular filtrate is normally reabsorbed in the proximal tubule of the frog and *Necturus*. After an adequate dose of phlorizin, this reabsorptive process is blocked and the glucose U/P ratio increased in consequence of the reabsorption of water. (Walker and Hudson [illegible])

normal animal, when the concentration of glucose in the glomerular filtrate is increased by raising the plasma level, the reabsorptive capacities of the proximal tubule are exceeded and the excess glucose is passed on through the distal tubule and excreted in the urine.[2270a]

It has long been known that the drug phlorizin causes glucose to be excreted in the urine of glomerular animals, a phenomenon attributed on the basis of other evidence to a specific action in

blocking tubular reabsorption.[illegible] Phlorizin does not affect the concentration of glucose in the glomerular filtrate of *Necturus*, but it does abolish the capacity of the proximal tubule to reabsorb it. In the phlorizinized animal, the glucose concentration increases perceptibly as the fluid passes down the proximal tubule (fig. 2). All the available evidence is contrary to the view that glucose is excreted by the tubules in any species, and the increasing U/P ratio may be attributed to the reabsorption of water.* Since under the action of phlorizin the glucose U/P ratio may reach 2.5 in the distal tubule, whereas this ratio does not exceed 1.4 in the proximal tubule, it follows that more water is reabsorbed in the distal than in the proximal system.

In contradistinction to chloride, phosphate is usually concentrated to a considerable extent by the kidneys of the frog and *Necturus*. Walker and Hudson [illegible] found that the phosphate U/P ratio rises progressively as the urine passes through the proximal and distal tubule, the greatest degree of concentration being effected in the latter. The final U/P ratios of phosphate (3.3) and of glucose (3.1) in phlorizinized *Necturi* are so nearly alike that it may be concluded that there is sufficient reabsorption of water to account for the concentration of phosphate, even if some of the glucose escaped by diffusion, as suggested above.

Although phosphate is usually concentrated by the tubules (though never to an extent greater than glucose under phlorizin), when the plasma concentration is very low it may be almost wholly absent from the urine. In such instances it is reabsorbed by the distal tubule.[illegible] Later evidence will show that the mechanism of phosphate reabsorption resembles that of glucose; when

* If it is assumed that phlorizin had completely blocked the reabsorption of glucose, the relative amount of water reabsorbed from the glomerular filtrate could be calculated from the U/P ratio of glucose, but Walker and Hudson c not believe that such is the case, on the basis of experiments in which gluco solutions were perfused through the tubules of phlorizinized *Necturi* they cor cluded that some of the sugar escapes through both the proximal and dista tubule by diffusion That phlorizin does increase the permeability of the tubules in the Amphibia sufficiently to permit glucose to escape from the tubular urine by diffusion is confirmed by the clearance experiments of Forster and his coworkers, who find that in the frog [illegible] and turtle [illegible] the glucose and creatinine clearances are only about 80 per cent of the inulin clearance, but no dissociation of the creatinine and inulin clearances is observed in phlorizinized mammals.

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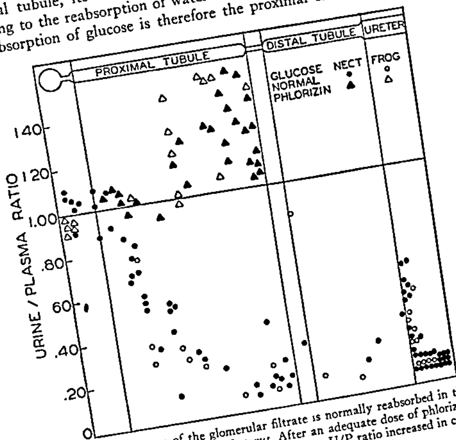


FIGURE 2 The glucose of the glomerular filtrate is normally reabsorbed in the proximal tubule of the frog and *Necturus* After an adequate dose of phlorizin this reabsorptive process is blocked and the glucose U/P ratio increased in consequence of the reabsorption of water. (Walker and Hudson[2343])

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the amount filtered is in excess of the reabsorptive capacity of the distal tubule the excess is excreted in the urine.

That, in the frog, urea is excreted in part by tubular activity was first suggested by Marshall [1396] on the basis that the final U/P ratio (bladder urine) of urea may reach 20 to 34, whereas the simultaneous U/P ratio of the pentose, xylose, which is only slightly reabsorbed,* never exceeds 3.0. In Walker and Hudson's [2134 2135] studies, the U/P ratio of urea, by the time the bladder was reached, attained an average value of 7.8, whereas the U/P ratio of glucose in phlorizinized animals, and of phosphate in normal animals, did not exceed 2.7. Hence these investigators concur with Marshall that in the frog some urea is excreted by tubular activity.† It should be emphasized that such tubular excretion is in addition to glomerular filtration and does not diminish the importance of the latter.

In contrast to the frog, in phlorizinized *Necturi* the urea U/P ratio is rarely greater than that of phosphate or glucose after phlorizin; ‡ the reabsorption of water appears to be sufficient in this species to account for the maximal tubular concentration of urea.

The urine in Amphibia is typically acid. Montgomery and Pierce,[1469] using the microquinhydrone electrode to measure the pH of the tubular urine, found that acidification takes place exclusively in the distal tubule, confirming the earlier observations of Richards [1705] that phenol red solution introduced into the tubule changes from red to yellow only after it has entered the distal segment. The cells that possess the power of acidification occupy slightly less than one-fifth of the total length of this segment and are situated somewhat nearer the distal than the proximal end. Though they show no outstanding histological fea-

* Reasons for believing that there is very little reabsorption of xylose, even in normal animals, are given in chapter IX.

† This conclusion is fortified by two additional facts: the rate of urea excretion (UV) in frogs requires an average glomerular filtration rate greater than is normally observed, and the rate of excretion is not directly proportional to the plasma concentration (P). This last point indicates tubular excretion because were only filtration involved, UV should increase in proportion to P.

‡ This statement should be qualified, because phlorizin is known to block the tubular excretion of some substances

tures, their location usually coincides with an abrupt widening of the lumen. Their activity is remarkable, for they can change the reaction of a 0.33 M sodium phosphate buffer from 7.5 to 6.8 in one minute; this is equivalent to adding one-fourth volume of 0.33 N hydrochloric acid to this buffer, and exceeds by 100-fold the increment in acid required to effect acidification of normal tubular urine.* †

Ammonia does not appear in the tubular urine of the frog or *Necturus* until the latter two-thirds of the distal tubule is reached (fig. 3).[2130] Within this region (and possibly also in the early part of the collecting duct) the ammonia concentration gradually increases until it approximates that of the bladder urine. Since ammonia is practically absent from the blood, its accumulation in the tubular urine must be the result of tubular synthesis, the tubule cells elaborating it from some unidentified precursor.‡ That the precursor is a cellular constituent is indicated by the fact that ammonia excretion continues when the kidney is perfused with a fluid containing no known ammonia precursor.§

Observations of this type have been extended to the guinea pig, rat, and opossum by Walker, Bott, Oliver, and MacDowell.[2131, 2137]

Glomerular puncture is difficult in mammals because the glomeruli are all below the surface of the kidney, and puncture experiments must generally be of a random nature, utilizing subsequent examination of the tubule to identify the site. However, the composition of the fluid withdrawn from a few glomeruli or from the first part of the proximal tubule indicates that the

* Ellinger[497] believes, on the basis of experiments involving the indicator fluorescein, that acidification occurs exclusively in the distal tubule of the frog [illegible]

[illegible]

nitrogen of some other amino acids

§ Willbrandt[2314] has reported on electrical potentials across the tubules of *Necturus*. Such potentials arise wherever there is an ionic concentration difference and are difficult to interpret at the present time.

psular fluid in the mammals, as in the Amphibia, is a true trafiltrate, with respect to glucose, creatinine, osmotic pressure, aloride, sodium, and phosphate (figs. 4 and 5).

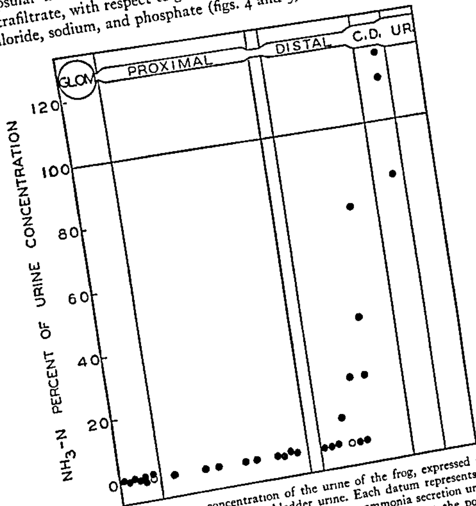


FIGURE 3. The ammonia concentration of the urine of the frog, expressed as per cent of the concentration in the bladder urine. Each datum represents a separate experiment. Note that there is apparently no ammonia secretion unt the first quarter of the distal tubule has been passed, or at about the poir where the urine is acidified. (Walker[3130])

Glucose is normally reabsorbed by the proximal tubule, just in the Amphibia (fig. 2). After the administration of phloriz glucose undergoes considerable concentration in the proxin tubule; when 50 per cent of the tubule has been traversed

glucose U/P ratio has risen to between 2.5 and 3.0. Creatinine is similarly concentrated in the proximal tubule in the normal animal, and on the assumption that it is not excreted by the

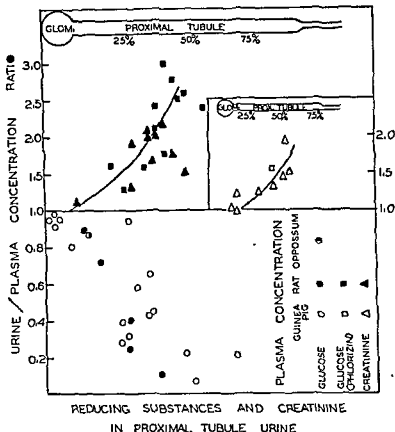


FIGURE 4 In mammals glucose is normally reabsorbed in the proximal tubule, as in the Amphibia. Phlorizin blocks this reabsorption and leads to a glucose U/P ratio ranging up to 3 at the middle of the proximal tubule as water is reabsorbed Creatinine, which is not reabsorbed by the tubules, is concentrated to about the same extent

The inset shows data on the guinea pig separately, because the U/P ratios are of a different order in the proximal tubule The curves are drawn to indicate the U/P

per cent (inset

per cent of the

tubule * the rise in the glucose U/P ratio in the phlorizinized animal may be attributed to the tubular *reabsorption of water.*

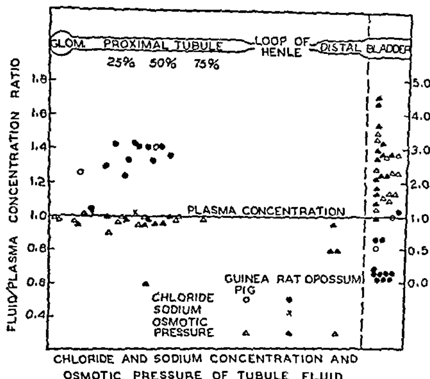


FIGURE 5 As in the Amphibia, in the mammals the osmotic pressure of the urine remains nearly identical with that of the plasma throughout the length of the proximal tubule Only three observations are available from the distal tubule, but they indicate that the urine may be dilute in the early part of this segment. It has, however, become osmotically concentrated by the reabsorption of water by the time the bladder is reached.

Chloride is slightly concentrated in the proximal tubule (U/P ratio of 1 4) but has been reabsorbed in the distal system. (Walker, Bott, Oliver, and MacDowell [2131])

Walker *et al.*[2131,2137] found that, of 41 specimens of fluid taken from glomeruli or proximal tubules, there was less than 0.08 per cent of protein (the minimal detectable concentration in some experiments) in 17, and less than 0.03 per cent in 8. Sixteen

* Creatinine is excreted by the tubules in man and the anthropoid apes, but not in the dog, sheep, rabbit, or seal, and it is presumed that it is not excreted by the tubules of the guinea pig or rat.

specimens gave positive protein tests; 14 of these contained less than 0.2 per cent and 9 less than 0.08 per cent. These figures are to be compared with an average protein concentration of 7 per cent in plasma, and they confirm the belief that in mammals, as in cold-blooded animals, the normal glomerular fluid contains either no protein, or at most very small amounts (less than 0.03 per cent).

Similar amounts of water appear to be reabsorbed per unit of tubule length Walker *et al.* estimate that in rats about 12.5 per cent, in guinea pigs about 7.5 per cent, of the fluid of the glomerular filtrate is reabsorbed by each 10 per cent of the first half of the proximal tubule It is technically impossible in mammals to collect fluid from the lower end of the proximal tubule, but it is estimated that at this point some 80 per cent of the filtrate will have been reabsorbed. This degree of reabsorption would lead to a creatinine U/P ratio of 5.0 (1 0/[1.0 − 0.8]). Thus water reabsorption is much more extensive in the proximal tubule in mammals than in Amphibia, a fact no doubt correlated with the relatively greater importance of glomerular filtration in the former.

The osmotic pressure of the proximal tubule urine remains identical with that of the plasma (fig. 5), as in the Amphibia, showing that the reabsorption of fluid in the proximal tubule is an isosmotic operation; i e. electrolytes, etc., are reabsorbed *pari passu* with water. Since the osmotic pressure of the bladder urine in mammals may be much greater than that of plasma, water must be reabsorbed against osmotic pressure in the distal system.*

The chloride concentration of the proximal tubule urine rises early to about 40 per cent above that of the plasma; since the osmotic pressure is the same, this implies that some other anion, presumably bicarbonate, has been reabsorbed.

These exquisite microchemical observations have done much to clarify the mechanism of urine formation in the forms studied. Combining all results in the Amphibia and mammals,† they specifically show that:

* The Amphibia cannot elaborate a urine hypertonic to the blood; this capacity appears only in the birds and mammals

† A warrantable equation, since the proximal and distal segments in the amphibian kidney appear to be homologous with these segments in the mammals.

1. the capsular fluid is formed by a simple physical process of ultrafiltration, through a semipermeable filter (the endothelium of the glomerular capillaries plus the basement membrane) that permits all plasma constituents except those of large molecular weight or macroscopic size, such as the plasma proteins, fat droplets, and formed elements, to appear in the glomerular urine in the same concentration per unit volume of water as they are present in the plasma in the case of non-electrolytes, or in such concentrations as will be determined by the Donnan equilibrium in the case of electrolytes;

2. glucose and phosphate are normally reabsorbed by the proximal tubule;

3. some water (40 per cent in Amphibia, perhaps 80 per cent in mammals) is reabsorbed by the proximal tubule;

4. simultaneously with the reabsorption of water, chloride (and attendant sodium) is reabsorbed by the proximal tubule to such an extent that

5. *the proximal tubule urine remains isotonic with the plasma*; *

6. but considerable additional water is also reabsorbed in the distal tubule, thus producing the final, concentrated bladder urine;

7. *the hydrogen ion concentration remains unchanged in the* proximal tubule, the urine being acidified in a sharply localized portion of the distal tubule;

8. *ammonia is synthesized and excreted by the distal tubule;*

9. in the frog *only* (among species so far examined) urea is excreted by the proximal tubule, in addition to being filtered.†

The microchemical technique suffers from the deficiency that it is impossible by direct measurement to ascertain how much water is filtered by any glomerulus (or by all the glomeruli *together) and therefore it is impossible to determine* how much water is reabsorbed by the tubules. In the absence of this knowledge, definite conclusions cannot be drawn about the precise *extent of tubular reabsorption or tubular excretion of any other* substance.

* The evidence indicates that the reabsorption of sodium is the primary, *active operation and that* the reabsorption of water is secondary and may be attributed to passive osmotic diffusion.

† The frog is an outstanding exception in this respect Urea is not excreted by the tubules in any mammal studied so far.

To put the problem in general terms: in order to know whether any substance undergoes tubular reabsorption or excretion, it is necessary to have, as a *standard of reference, some substance which is known not to undergo tubular reabsorption or excretion.* Then the change in concentration that the substance undergoes in passing down the tubule will reveal the extent of water reabsorption, since the U/P ratio will be dependent only upon water reabsorption. If any other substance *simultaneously* present in the blood and urine is concentrated to a lesser or greater extent than the standard of reference, this can only be a result of the tubular reabsorption or tubular excretion of the second substance. In the experiments cited above it might be assumed that the reabsorption of glucose is completely blocked by phlorizin, thus satisfying the foregoing requirements. But doubt has been expressed that such is the case in the frog and *Necturus*, since the evidence indicates that phlorizin so injures the tubules that some glucose escapes by diffusion. Such has been shown to be the case in the frog by clearance studies,[674] and, apart from this circumstance, there remains the possibility that phlorizin may also impair tubular reabsorption or excretion of other substances, or indeed alter the filtration rate by action on the glomerular arterioles, and its use is therefore limited.

In chapter IX the question of an ideal standard of reference for water reabsorption will be discussed in detail, but it is first necessary to consider the phenomena of tubular excretion

TUBULAR EXCRETION

Evidence has been cited above that, in the frog, urea is excreted by the tubules in addition to being filtered by the glomeruli The reality of the tubular excretion of other substances has been clearly demonstrated by numerous students of comparative physiology, and particularly by studies on the aglomerular kidney of certain marine fishes (*vide infra*), and it is now known that tubular participation is involved in the excretion of a number of important substances in man. The only generalization that can be made is that tubular excretion of any substance is a possibility in any species and can only be excluded by examination. A discussion of the evidence on tubular excretion from comparative physiology

is therefore chiefly of historic interest and may be omitted by the student who is pressed for time in favor of the specific problem of how to measure the filtration rate.

THE NUSSBAUM EXPERIMENT

Much of the older evidence adduced for tubular excretion was based on experiments with the frog's kidney In 1878 Nussbaum proposed to take advantage of the renal-portal circulation in the frog by ligating the aorta or the renal artery and injecting into the renal-portal vein various substances the excretion of which he wished to follow. In 1906 Cullis improved the experiment by the perfusion of the arterial and venous systems separately. The original Cullis experiment has been modified to permit the perfusion of arteries, veins, or both, at definite pressures; by one modification or another, many attempts have been made to obtain evidence on the relative function of the glomeruli and tubules, and an extensive literature has accumulated on this subject [596, 1859]

However, it has been shown by Richards and Walker,[1716] Hayman [935] and others that the glomeruli are available to the portal perfusion fluid by way of anastomoses within the kidney, and Kempton [1109] has shown that after the renal artery is ligated the perfusion fluid can reach glomeruli by way of collateral arteries from the ureters Consequently, any experiment in which restriction of the perfusion fluid to definite parts of the kidney is assumed must be interpreted with caution.

In addition to perfusion experiments, a large literature has accumulated on the microscopic observations of the renal tubules during the excretion of dyes. But all experiments in which dyes are demonstrated to be present in the tubule cells of glomerular kidneys are suspect since the dye may gain access to the cell by way of the lumen Dyes may also be taken up by the tubule cells from the interstitial fluid without being excreted subsequently into the lumen; i e their properties are such that they act as vital stains and are stored in the cell. Consequently, phenomena of vital staining and the mere renal extraction of dyes from the blood have an uncertain bearing upon tubular excretion.[763, 1553, 1554, 1672] Indeed, it appears that substances which are either excreted or reabsorbed by the tubules do not accumulate to any detectable extent in the tubule cells—they are whisked through with lightning-like rapidity. Because of their possible ambiguity, experiments such as those above will not be considered here.

THE AGLOMERULAR KIDNEY

In 1902 Huot discovered that the kidneys of certain marine teleost (bony) fishes contain no glomeruli, and subsequent investigations have considerably extended the list of aglomerular species. In some families of marine teleosts there may be numerous and well-developed glomeruli; in other families the glomeruli may be very few or very poorly developed, and in still others they may be entirely absent.[1408] In some fishes there are a few glomeruli that are functional in the young animal but degenerate in the adult stage.[839 843]

The evolution of the aglomerular kidney in the marine teleost has been interpreted by Marshall and Smith[1408 1974, 1931] as an adaptation to hydropenia and oliguria associated with a sea-water habitat Sea water is hypertonic to the blood of all vertebrates other than the elasmobranch fishes, and the teleost fishes must obtain their water for urine formation by drinking the salt water and excreting the bulk of the salt through the gills at considerable cost in osmotic work. Consequently, water is excreted as sparingly as possible, and since glomerular filtration is the first step in water excretion—indeed the glomeruli appear to have been evolved in the vertebrates as an adaptation to their early fresh-water habitat[1931]—glomerular function is reduced to a minimal level. The aglomerular condition may be considered a terminal state in the progressive degeneration of glomerular function among the marine teleosts, and there is no reason to believe that the functional capacities of the aglomerular tubules * are essentially different from those of the glomerular kidney.

In 1928 Marshall and Grafflin[834, 1402] and Edwards[871] undertook the functional examination of the aglomerular kidney Marshall and Grafflin serially sectioned the kidney of the goosefish (*Lophius piscatorius*) and demonstrated that it can be considered to be truly aglomerular, although it contains about 1 non-functional, pseudoglomerulus to every 2000 tubules A little later the kidney of the adult toadfish (*Opsanus tau*) was shown by Grafflin[833] to be entirely aglomerular, and Armstrong (pers. com) has shown that a glomerulus does not develop in the embryonic pronephros in either this species or the pipefish. The whole function of this kidney is performed by blind tubules made up of high or cuboidal epithelium possessing brush border and corresponding closely to the proximal segment of the amphibian and mammalian tubule (plate III) It has a structure that points strongly in the direction of highly specialized chemical operations, with nothing comparable to the filtration

* In at least certain aglomerular forms only the proximal tubule is present.[839]

apparatus of the glomerulus. The blood supplied to these aglomerular tubules is venous and probably has a hydrostatic pressure lower than the osmotic pressure of the plasma proteins, so that it is difficult to imagine how filtration could occur.

It has been shown in these studies of the goosefish, in Marshall's subsequent study of the toadfish,[1391, 1403] and in Edwards and Condorelli's [676] *study of the pipefish and sea horse, that the aglomerular kidney* can excrete most of the ordinary urinary constituents: water, creatine, creatinine, urea, uric acid, magnesium, sulphate, potassium, and chloride, and, among foreign substances, iodide, nitrate, thiosulphate, thiocyanate and the dyes indigo-carmin, neutral red, and phenol red Estrogens, free or conjugated, are excreted in the urine of the aglomerular toadfish.[201] It is obvious that the water of the urine must also be excreted by the tubules of the aglomerular kidney. That this is the result of active tubular transport is shown by the fact that the maximal urine 'secretion' pressure in the toadfish may be higher than that of the dorsal aorta and 4 or 5 times the venous blood pressure (only venous blood supplies the kidney).[157]

In view of this highly developed excretory capacity for some substances, it is the more significant that the aglomerular kidney is unable to excrete certain other substances, among which are ferrocyanide, glucose,[1392, 1396, 1402] and the dye cyanol,[1016] (all of which are readily excreted by the glomerular kidneys of other animals) and albumin,[158] which, under certain circumstances at least, is excreted by glomerular kidneys. Even when large doses of glucose are given to raise the blood level, along with maximal doses of phlorizin, the urine of the aglomerular fish remains glucose-free Subsequent investigations have shown that xylose,[391, 1075] lactose,[1396] sucrose,[1925] and inulin,[1720, 1845] all of which are readily excreted by glomerular kidneys, are not excreted by the aglomerular kidney.

The aglomerular kidney shows the phenomenon of a 'threshold' in the sense that chloride may disappear from the urine under some conditions and under others it may be present in large amounts Other substances (creatine, phenol red, sulphate, magnesium) may be present in the urine in concentrations many times the simultaneous concentrations in the plasma, a circumstance requiring the expenditure of energy in the excretory process, energy which is presumably derived from the metabolism of the tubule cells. The rate at which phenol red and creatinine can be excreted by the toadfish kidney has an upper limit,[169, 1403] implying physiological limitations in the excretory mechanism that would not be present in a simple process of ultrafiltration. Certain

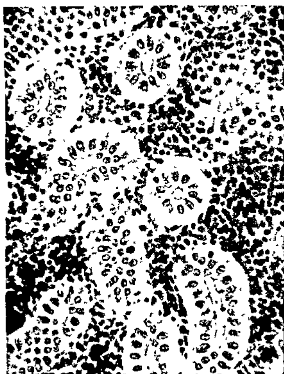


PLATE III. Aglomerular kidney of the toadfish, *Opsanus tau* The aglomerular tubules, which consist entirely of the proximal segment, are separated from each other by lymphoid tissue, the function of which is unknown The cuboidal nature of the cells, which are essentially uniform throughout the tubule, is particularly to be noted as contraindicating a process of filtration such as occurs in the capillary tuft of the glomerular kidney

of tubular excretion This *phenomenon* is displayed *only* by *the* cells of the proximal tubule, the distal tubule showing no capacity to excrete phenol red or other dyes.

Lowering the temperature of the culture to between 3 and 6° C. stops *the tubular* excretion of *both* water and phenol red, as also do hydrocyanic acid, hydrogen sulphide, anoxia, and sodium iodoacetate, but carbon dioxide has little effect The pH of the cyst fluid in which the phenol red is concentrated is greater than 8.0, while the cytoplasm of normal tubule cells appears to be nearly neutral, pH 6.8 ± 0.2. The cyst fluid, which accumulates under slight positive hydrostatic pressure, is normally moderately hypotonic to the protein-free culture medium, and its formation is accelerated by the presence of phenol red or magnesium sulphate in the medium, recalling the diuresis produced by similar compounds in the aglomerular fish [113, 339, 340, 342, 1214]

Van Deen and De Haan [2087] have confirmed the tubular excretion of phenol red by the chick metanephros and have extended the observations to trypan blue, which apparently diffuses through necrotic cells to accumulate in the tubular urine by combination with protein.

Forster [679] and others [1571] have employed *in vitro* preparations of fish kidney (sculpin, flounder, trout) and of the kidney of higher animals in the study of the transport of phenol red, using micromethods for the determination of the concentration of the dye in the lumen. The method is particularly advantageous for studies on the physiological and biochemical nature of cellular transport systems In the sculpin the nephron is composed entirely of the proximal segment, as in the aglomerular fishes.

Little is known about the nature of this tubular transport system. There is no reason to believe that the energy of the circulation can be used for tubular excretion, and it must be inferred that this energy is supplied by the metabolism of the tubule cells. Unlike tubular reabsorption, which involves a number of independent transport systems, tubular excretion apparently involves only two, since so far as is known *all* substances excreted by the tubules mutually depress the excretion of other substances in one of these two groups by competition within the transport system.

CHAPTER III

Measurement of the Filtration Rate

THE CONCEPT OF RENAL CLEARANCE *

It will facilitate subsequent discussion if at this time we introduce the concept of renal clearance, an expression that has come into widespread use as a quantitative description of the rate at which the kidney excretes various substances relative to their concentration in the plasma.

If U_x is the concentration of x in each cc. of urine and V is the rate of urine formation in cc/min., then U_xV = the rate of excretion of x in mg/min. If P_x is the concentration of x in each cc of plasma, then U_xV/P_x = the volume of plasma required to supply

* The term 'clearance' was first used [illegible] a virtual rather than a real volume. Möller, McIntosh, and Van Slyke did not attempt to explain the urea clearance in terms of any particular process in the kidney. They were primarily interested in obtaining a mathematical [illegible]

the quantity of x excreted in each minute's time. The expression U_xV/P_x (or, as it is commonly written for brevity, UV/P) is called the *plasma clearance* of x. Alternatively, we may say that UV/P, or the clearance of any substance, is the *virtual* volume of plasma completely cleared of that substance in one minute's time.*

To take specific data for illustration, the plasma contains 93 per cent water, and the average rate of water excretion (urine flow) in man is about 1 cc/min. (UC = 1.0); hence we may say that 1.0/0.93 or 1.07 cc. of plasma are cleared of water per minute. When, under conditions of constant plasma concentration and accurate urine collection, the excretion of other substances is examined, it may be found that in one subject 10 cc. of plasma are simultaneously cleared of sulphate, 20 cc. of potassium, 67 cc. of urea, 130 cc. of inulin, 450 cc. of phenol red, and 660 cc. of diodrast per minute.

These figures tell us nothing about how these substances are removed from the plasma into the urine, whether by filtration plus tubular reabsorption, filtration alone, or filtration plus tubular excretion. Thus we come to the problem posed in the preceding chapter—the need for some substance that is completely ultrafiltrable through the glomeruli and is neither reabsorbed nor excreted by the tubules. Given such a substance, F (for filtration), then the plasma clearance of F will be identical with the filtration rate; if there is 0.10 mg. of F in each cc. of plasma, and if 130 cc/min. of plasma are filtered, 13 mg. of F per minute will pass into the glomerular filtrate and, undergoing no reabsorption or addition, will appear in the urine; i.e. $U_FV = 13$ mg/min., and $U_FV/P_F = 130$ cc/min. Thus the plasma clearance, C, of this substance (C_F) will be equal to the filtration rate.

* The concentration of x in *whole blood*, or the *whole blood clearance* (UV/B), should not be used unless x penetrates the red cells and, as the blood traverses the kidneys, the red cells are simultaneously completely cleared of x, which is true of no known substance. If the red cells are partially cleared by x, a correction factor may be applied to the plasma clearance, but actually there is no important instance known in man where any substance is removed even in part from the red cells during passage through the kidney. Only the plasma is 'cleared' by glomerular filtration, and in general only the plasma is cleared by tubular excretion, and hence plasma clearances are always to be preferred.

This inductive argument is simple and obvious enough, though actually nearly 100 years of renal physiology elapsed after Ludwig propounded his theory of glomerular filtration before the argument was set into words or put to experimental examination. The reason for the delay is clear: there were no biochemical methods applicable to small quantities of blood throughout most of this period, and the methods applicable to urine were relatively few. Until Bang, Folin, Benedict, Van Slyke, and others developed microanalytical methods to be used on protein-free plasma filtrates, renal physiologists were largely restricted to studying the volume, specific gravity, and freezing point of the urine. With each increment in analytical technique and factual knowledge the principles underlying renal physiology took clearer form, until it was recognized that a precise, quantitative method of measuring the filtration rate was not only a possibility but a necessary attainment if progress were to be made in this field. The first to appreciate this fact was Rehberg,[1888] who in 1926 recommended exogenous creatinine for this purpose, on the grounds that this substance was concentrated in the urine to a greater extent than any other known substance. Subsequent work, however, has demonstrated that creatinine is in part excreted in man by the tubules. Within the past 15 years numerous substances have been studied in a variety of animals and man, and although creatinine is satisfactory in most mammals, the choice standard of reference is, for a number of reasons, the polysaccharide inulin mentioned above.

MEASUREMENT OF RENAL CLEARANCES

For the determination of a consecutive series of renal clearances, the substance under examination, if foreign to the body, must be administered first in a priming dose to establish approximately the desired plasma concentration, and then at a constant rate by intravenous infusion to keep the plasma concentration at the desired levels. Some substances, the renal clearances of which are not too high (creatinine), may be given subcutaneously in dogs and small animals. In the dog and man it is desirable to insert a retention catheter in the bladder and to collect urine throughout carefully timed intervals (10 to 15 min.), the bladder being emptied by suprapubic pressure and if necessary rinsed with

measured volumes of saline introduced by syringe, the last of the urine or rinsing fluid being expelled by 10 or 15 cc. of air. (Rigidly sterile technique should always be used in man and male dogs, but is unnecessary in female dogs, which are highly resistant to bladder infection.) Samples of blood are drawn at more widely spaced intervals (*c.*30 min.) and centrifuged *at once*. Diuresis is generally induced by the oral administration of tap water (up to 1 liter in man or 100 cc/kg. in dogs in 2 doses) 45 to 60 min. before the first urine collection period. If the bladder is rinsed, as is always desirable when the urine flow is small, the volume of washout fluid is deducted from the total volume in order to calculate the true urine flow, V, and the washout dilution is incorporated with subsequent laboratory dilutions in the calculation of the true urine concentration, U.*

After analysis, the observed plasma concentrations are plotted on semi-logarithmic paper against time and the precise values (P) at 2.5 to 5 min. before the middle of each urine collection period are determined by interpolation.† This 2.5 to 5 min. correction (delay time) is to allow for the time elapsing between the collection of a peripheral sample of blood (usually venous) and the arrival in the bladder of urine formed from that blood. The clearance of any substance is then calculated by the formula, UV/P.

Because of differences in the development and functional activity of the kidneys in different individuals, it cannot be expected that the clearance of any substance will be the same in two individuals, nor will one individual show the same clearance for any substance under all circumstances. Hence in comparing

* A major source of error in the clearance method lies in the difficulty of emptying the bladder completely, or of knowing the exact moment at which emptying is achieved. These difficulties introduce random errors in the V term, so that the figure for one clearance period may be slightly low and the next one slightly high

† The *true mean* concentration, where dP/dt is exponential, is actually

$$\frac{P_1 - P_2}{2.3 \log \frac{P_1}{P_2}}$$

but for most purposes *graphical interpolation is adequate.*

the excretion of two or more substances, it is necessary, even under the best physiological conditions, to observe *simultaneous* clearances. Since errors in the V term affect all simultaneous clearances proportionally, it is advantageous when comparing the excretion of two substances to consider the *clearance ratio*, which has the effect of cancelling out the V term and the errors associated with it:

$$\frac{U_1V}{P_1}\bigg/\frac{U_2V}{P_2} = \frac{U_1}{P_1}\bigg/\frac{U_2}{P_2}$$

Wherever two clearances are compared, or wherever a clearance ratio is cited, it is understood that the clearances are determined *simultaneously*. Though the clearance of any substance may be used as a standard of reference, it is logical to take the glomerular clearance (inulin clearance in man, inulin or creatinine clearance in the dog) for this purpose.

Absolute values of renal clearances are not highly significant except when they are the average of several consecutive periods (3 is a good number), and even in the same individual the average clearances must be interpreted with caution pertinent to the interpretation of biostatistical data of any kind

It is unnecessary to describe here the chemical procedures used for the analysis of the plasma and urine, which should, of course, be adapted to yield the highest possible accuracy.* To illustrate a specific example, a series of urea, inulin, and p-aminohippurate (PAH) clearance determinations in a normal man are summarized in table 1. No urea was administered because there was a sufficient concentration of this substance already present in the plasma. Without for the moment dwelling upon the absolute values of these clearances, attention is called to the fact that they differ markedly in magnitude. To apply the definition of clearance, it may be said that the average minimal (or nominal) volumes of

* Detailed protocols for the measurement of the filtration rate, renal blood

the two now in use are the diphenylamine method [795] and a modification of the Roe resorcinol method [1801]

TABLE I

Simultaneous Urea, Inulin, and p-Aminohippuric Acid (PAH) *Clearances in a Normal Man*

(All clearances and V corrected to 1 73 sq. m. surface area Subject drank 1000 cc of water between −92 and −62 min.)

Elapsed time from priming min.	Urine volume cc/min	Plasma			Urine			Clearances			Clearance ratios	
		Urea mg/cc	Inulin mg/cc	PAH mg/cc	Urea mg/cc	Inulin mg/cc	PAH mg/cc	Urea cc/min.	Inulin cc/min	PAH cc/min	Urea/Inulin	PAH/Inulin
28 0	Urine discard											
39 0	2 80	0 212	0 262	0 0175	5 68	125	4 40	75 0	134	704	0 560	5 25
50 5	3 20	0 210	0 258	0 0168	5.16	116	3 97	78 6	144	756	0 546	5 25
62 0	2 60	0 209	0 250	0 0162	5 54	122	4 23	68 9	127	679	0 543	5 35
72 0	2 80	0 207	0 240	0 0154	5 20	111	3 86	70 3	130	702	0 541	5 40
84 0	2 50	0 206	0.233	0 0148	6 36	130	4.44	77.2	140	750	0 551	5.36
104 0	2 50	0 205	0 222	0 0142	6 32	124	4 02	77 1	140	708	0 551	5 06
							Average	74.5	136	717	0 549	5.28

Wrong figures for Inulin

plasma required to supply the excreted urea, inulin, and PAH were, respectively, 74 5, 136, and 717 cc/min.*

PHYSIOLOGICALLY POSSIBLE EXCRETORY OPERATIONS

The actual value of the renal clearance of a particular substance reveals nothing about the physiological operations by which it is excreted. But the very fact that the clearances of various substances do differ reveals that the kidney must handle these substances by different means. Excluding chemical transformations, such as deamination, oxidation, etc., with which we need not be concerned at the moment, the excretion of a particular substance might in theory be effected by filtration alone, filtration plus tubular excretion, or filtration plus tubular reabsorption. Let us consider, first, a substance that is completely filtered through the glomerulus; in spite of the fact that this substance is present in the glomerular filtrate, if the tubules completely reabsorb it, its clearance will be zero (see A in fig. 6). If the extent of tubular reabsorption is progressively decreased, the substance will appear in the urine in progressively larger quantities and its clearance will increase (B and C) until, if there is no tubular reabsorption at all (F), the clearance (C_F) will be equal to the rate of glomerular filtration On the other hand, if a substance is excreted by tubular activity in addition to being filtered, its clearance will be greater than the rate of filtration by an amount equal to the extent of the tubular clearance (V, W, X). Obviously there is an upper limit to the possible range of clearance values because, excluding storage in the tubular cells, the kidneys cannot excrete more of a substance in any period than is brought to them by the blood; the upper limit of renal clearances is therefore equal to the (effective) plasma flow through the total excretory tissues of the kidneys

Thus, if each cc. of plasma contains 1 mg. of X, and if 700 cc. of plasma flow through renal excretory tissue each minute and are completely cleared of X (X being concurrently excreted in the urine), then 700 mg. of X will be excreted each minute and UV/P will equal 700. (The effective renal plasma flow divided

* In the publication of data it is conventional to omit urine concentrations, since these can be calculated from the recorded values of P, V, and UV/P

by the per cent plasma in the blood gives the effective renal blood flow.) Actually all types of substances mentioned are known: in man, A might be glucose; B, vitamin C; C, urea; F, inulin; V, creatinine; W, phenol red; X, p-aminohippurate.

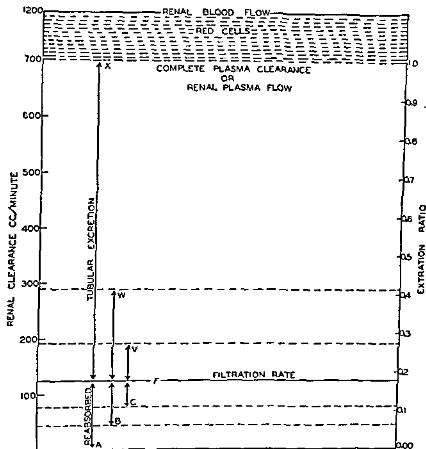


FIGURE 6. Schema illustrating the possible range of renal clearances

The fraction of any substance removed from the renal plasma during one circulation through the kidney is given by (A − V)/A, where A and V are the concentrations in arterial (or systemic venous) and renal venous plasma, respectively. This fraction is called the *plasma extraction ratio.** The extraction ratio of X (for

* When dealing with a substance such as urea, which penetrates the red cells, the extraction ratio will depend on the hematocrit and the cell:plasma ratio.

active excretory tissue) in the example above would be 1.0, and for all other compounds less than 1.0.

The ratio of glomerular filtrate and effective renal plasma flow, or C_F/C_X, will represent the fraction of plasma (measured as a virtual volume of plasma and not as water *per se*) that is filtered through the glomeruli, or the *filtration fraction*.

THE INULIN CLEARANCE AS A MEASURE OF GLOMERULAR FILTRATION

A standard of reference suitable for measuring the glomerular clearance must fulfil certain specifications:

1. It must be completely filtrable at the glomerulus; i.e. its molecular size must not be so great as to prevent its passing through the glomerular membrane, and it must not combine with or be absorbed by the plasma proteins, which are themselves unfiltrable.
2. It must not be synthesized or destroyed by the tubules.
3. It must not be reabsorbed or excreted by the tubules.
4. It must be physiologically inert, so that its administration does not have any disturbing effect upon the body, and particularly upon the kidneys. And it must of course be of such a nature that its concentration in plasma and urine can be determined accurately.

In regard to (1), numerous lines of evidence indicate that the upper limit of permeability of the glomerular membranes in mammals may be set at a molecular size somewhat under the plasma proteins (see ch. VIII). The filtrability of any substance can be demonstrated experimentally by ultrafiltration through collodion or other suitable membranes impermeable to the plasma proteins. When plasma itself is ultrafiltered, this method reveals adsorption on the plasma proteins, if such exists.

Exclusion of (2) is simple in the case of compounds that are wholly foreign to the body. Renal synthesis of compounds normally present in the urine is in some instances, such as ammonia, revealed by a clearance approximating or exceeding the renal plasma flow.

Exclusion of gross toxic action is also simple, and effects on the renal circulation can be excluded with reasonable confidence by reference to other clearances.

It is in regard to tubular reabsorption and tubular excretion that the greatest difficulty is encountered, for there is no way to examine these processes directly either in single nephrons or in the intact animal, and all conclusions must be based upon the relative behavior of several substances under a variety of conditions.

The evidence is now convincing that inulin fulfils the specifications for measuring glomerular filtration in all vertebrates. Since in the nature of the case this evidence must consist of a comparative study of the clearances of various substances, it will be convenient to defer detailed discussion until chapter IX. Because various substances have been used to measure the filtration rate (inulin, mannitol, thiosulphate in man, and creatinine, in addition, in the dog) it is convenient to indicate any acceptable, pure filtration clearance as C_F.

HISTORICAL NOTE ON THE USE OF CARBOHYDRATES AS INDICES OF GLOMERULAR FILTRATION

When the author and his coworkers undertook to discover a substance that would fulfil the specifications for the measurement of the filtration rate, they were guided by the following *a priori* considerations. Since it had been shown that the tubules of the aglomerular kidney can excrete magnesium, sulphate, chloride, creatinine, uric acid, phenol red, etc, it had to be assumed, in the absence of evidence to the contrary, that the tubules of other animals might also be able to excrete these and perhaps related substances. On the other hand, the fact that the aglomerular tubules cannot excrete glucose, although it does not prove that this substance cannot be excreted by glomerular tubules, offered a promising line of investigation. On broad principles it may be supposed that, being a food and not a waste product, glucose has been conserved by the vertebrates throughout their evolution, and at no time continuously excreted from the body. Consequently, the tubules have never been called upon to excrete it and they remain incapable of doing so. The presence of glucose in the urine of glomerular kidneys during hyperglycemia or after the administration of phlorizin could well be attributed to incomplete reabsorption from the glomerular filtrate Inasmuch as glucose is normally reabsorbed by the tubules, it can itself furnish no evidence on the rate of glomerular filtration unless the reabsorptive process is blocked by phlorizin; but since this drug may block other

tubular processes its use is of dubious value It seemed, however, that if glucose were not excreted by the renal tubules other sugars might not be excreted by them, and that among the metabolically inert carbohydrates one or more might be found that was not reabsorbed, as was this physiologically important foodstuff. With this thought examination was begun of the excretion of non-metabolized carbohydrates, xylose, sucrose, and raffinose, in normal and phlorizinized animals, in relation to the simultaneous excretion of urea, creatinine, etc The evidence is now convincing that, in the glomerular as in the aglomerular kidney, these substances are not excreted by the tubules, but the inference that there would be no tubular reabsorption has proved to be incorrect Earlier investigations [1078, 1923] indicated that xylose was not reabsorbed in the normal animal, but this conclusion had to be modified when the investigations were extended to inulin and it was found that the inulin clearance in normal animals is about 25 per cent higher than the simultaneous xylose clearance (see ch. IX) It is now thought that this discrepancy between the xylose and inulin clearances is due to the entanglement, so to speak, of the former in the glucose reabsorptive mechanism, since the discrepancy is removed by phlorizin

Experiments with inulin were begun independently by Richards, Westfall, and Bott [1720] shortly before our own investigations were started In both laboratories the line of investigation was directed by the desire o obtain a very large molecule, in order to minimize tubular diffusion, o that the tubular reabsorption of water could be measured as accutely as possible

PROPERTIES OF INULIN

ulin is a starch-like polymer, consisting principally of fructose, ch is almost insoluble in cold water. Inulin dissolves readily ot water, however, and, on cooling, forms supersaturated tions that may be administered intravenously. After intraus administration in dogs and man it is rapidly and comy excreted in the urine; [1720, 1868, 1948] Schwartz, Schachter, and kel [1811] found that over 95 per cent of the total amount red in 24 hr. is excreted in 9 hr. There are no enzymes in od capable of hydrolyzing it,* and it is probably excreted

biotte and Rosa (pers com) report that inulin does not penetrate the or amniotic membranes except during labor

in the urine quantitatively, except for traces that may be excreted in the bile.*[1016]

When properly prepared, inulin is physiologically inert and non-toxic in doses required for physiological investigations, even on repeated injection,[1050] and its intravenous administration in man produces no detectable change in renal function, circulation, etc., in doses as large as 160 gm. Commercial preparations, and even material that has been repeatedly recrystallized from water and ethanol, may contain considerable quantities of pyrogen, which in large doses will induce extreme fever and serious circulatory disturbances, and before use in clearance work, and particularly before administration to man, all inulin preparations should be tested carefully for pyrogenic action.†

The true molecular weight of inulin is about 5000,[2177] showing that it contains about 32 hexose molecules. This large molecular weight is important because it results in low diffusibility; actually the diffusion coefficient of inulin is considerably less than would be expected from its molecular weight, because of the fact that it is a very elongate molecule and elongation increases the effective radius under conditions of random orientation. The effect of elongation in the case of inulin is such as to produce a diffusion coefficient equivalent to a molecular weight of about 15,000.[292] The diffusion coefficients of several substances of physiological

* This point is important, not because it shows that the material is not metabolized, which would make no difference in renal clearance studies, but because it excludes the possibility of lower, reabsorbable polymers in the plasma Such lower polymers are formed by the action of blood amylase after the injection of low molecular-weight starches, a fact that precludes their use for renal function studies (unpubl obs)

† This pyrogen is of bacterial origin and appears to accumulate in the dahlia tubers before processing The contamination of inulin by pyrogen has been a most disturbing factor in its use, for purification has proved to be relatively difficult and has retarded its commercial preparation The dose of 160 gm. mentioned in the text was obtained from a 10 lb lot that had had no special treatment; this 160 gm. dose, the first to be administered to man, was taken by Dr Shannon with no subjective reaction whatever After 41 other clearance tests using this original lot, with no reaction, a new lot proved to be dangerously pyrogenic No other non-pyrogenic commercial preparation that has not had special treatment has ever been obtained by the author's laboratory. Artichoke inulin has not been commercially available in this country.[234, 237, 356, 788, 802, 893, 1934, 1936]

interest are shown graphically in figure 7.* Hemoglobin fails to pass through the glomerular membranes, presumably because of its large molecular size. Since the diffusion coefficient of inulin is only twice that of hemoglobin, it would appear that, for the purpose of reducing diffusion, little can be gained by seeking a molecule larger than inulin.

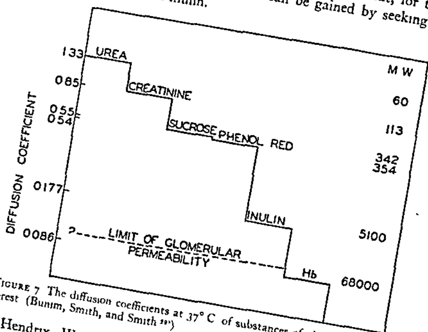


FIGURE 7 The diffusion coefficients at 37° C of substances of physiological interest (Bunim, Smith, and Smith [illegible])

Hendrix, Westfall, and Richards [977] have shown that inulin passes into the capsular fluid of frogs and *Necturi* in the same concentration as it is present in the plasma Shannon and Smith [1368] have shown that it is completely filtrable from human and dog plasma through collodion membranes, showing that it is not bound to plasma proteins, and it is amenable to accurate chemical analysis.

Exogenous creatinine is excreted by the tubules in man and the anthropoid apes, the chicken, and many cold-blooded animals,

* Bunim *et al* note that extrapolation of data given by Ohoem indicates a diffusion coefficient of 0.89, 0 51, 0 53, 0 15, and 0 12 for arabinose, maltose, [sucro]se, dextrin, and starch, respectively

but it will be shown in chapter IX that the creatinine and inulin clearances are identical in most mammals, and for practical reasons this substance is generally used in the dog, rabbit, cat, etc., in place of inulin.

GLOMERULAR CLEARANCE

In man and the dog the rate of glomerular filtration is relatively constant, under standard conditions, and independent of the urine flow. The renal blood flow may vary considerably from day to day in both species, but the renal circulation is highly autonomous, effecting its own adjustments independently of the central nervous system, and it tends to be quite stable under standard conditions. The mechanism of the glomerular circulation is such that, by differential constriction of the afferent and efferent arterioles, glomerular pressure and hence the filtration rate are maintained nearly constant within a wide range of renal blood flow. Hence the filtration rate is even more stable than the renal blood flow.

Data showing the filtration rate at various urine flows in man and the dog are given in figures 8 and 9 * In the data on man,[363] each point represents a single clearance period of 10 to 40 min. duration, the observations being made in groups of 5 to 10 at about weekly intervals under standard conditions (i.e. before breakfast, with the subject recumbent in bed, and after hydration by a liter of water 60 to 90 min. before the first clearance period). A wide range in urine flows was obtained by keeping the subject on a low or high water intake and by the administration of varying quantities of water on the morning of observation. The data in figure 9 are from Shannon's [1850] study of the dog, in which the creatinine clearance was used as a measure of the filtration rate. Except for the fact that the dog cannot be observed under as constant, standard conditions as can man, the arrangement of the experiments was much the same. Slight variations in clearances from period to period may be attributable in part to errors in the collection and timing of urine samples or to analytical errors.

* The simultaneous urea clearances are included in these figures to show that they behave in a manner roughly parallel to the inulin clearance. The fact that the urea clearance is lower than the inulin clearance reveals that a considerable fraction of the filtered urea is reabsorbed by the tubules (ch. IV).

In both man and the dog, the rate of glomerular filtration at low urine flows, obtained under conditions of dehydration, tends to decrease probably because of a decrease in the volume of extracellular fluid below the average level to which the filtration rate seems normally to be physiologically adjusted. At very high urine flows, obtained under conditions of excessive hydration, the

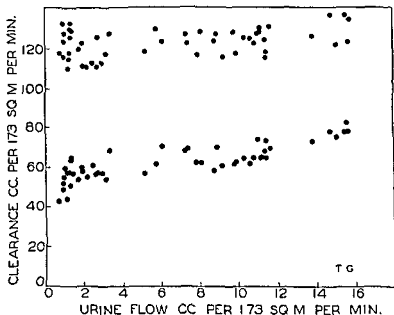


FIGURE 8 Simultaneous inulin (above) and urea clearances (below) in man at constant or decreasing urine flows (Chasis and Smith [363])

filtration rate tends to increase above the average, probably because of expansion of the extracellular fluid. The important question is whether or not these changes in filtration rate between oliguria and extreme diuresis are an intrinsic part of the mechanism of diuresis. With a filtration rate of 130 cc/min. in man, only small variations, scarcely beyond experimental error, would be required to account for a change in urine flow from 1 to 5 or even 10 cc/min. The answer to this question in the minds of most investigators [363, 441, 894, 1030, 1850] is no, for the following reasons:

a. It is possible by careful changes in hydration to vary the

urine flow by the administration of water through the physiological range of diuresis (in man from slightly under 1.0 up to 10 or 12 cc/min.) without changing the filtration rate.

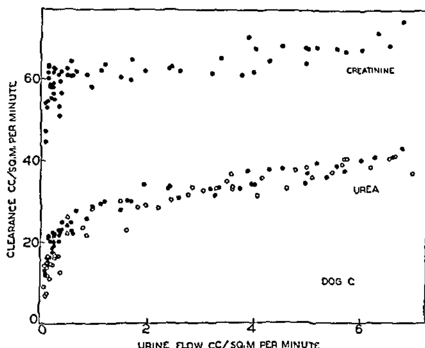


FIGURE 9. Creatinine and urea clearances in the dog, in relation to urine flow, as observed when the latter is constant or decreasing. Each point is a single clearance period uncorrected for surface area (sic) The upper data represent creatinine clearances, the lower data urea clearances The circles in the lower data represent urea clearances in the absence of administered creatinine, the dots urea clearances in the presence of administered creatinine. The data were obtained on a low protein diet. (Shannon [1850])

b. The urine flow varies throughout the physiological range of diuresis in response to varying hydration, regardless of the absolute value of the filtration rate. This is particularly evident in the dog, where the filtration rate may be increased by 60 per cent or more on a high as compared with a low protein diet, without influencing the phenomenon of water diuresis.

c. A highly specific mechanism in the pituitary gland (involving the secretion of the antidiuretic hormone) controls the urine

flow throughout the normal diuretic range and operates independently of the filtration rate, over which it has no demonstrable control, by regulating the quantity of water reabsorbed by the renal tubules, regardless of the value of the filtration rate.

The filtration rate under standard conditions is fairly constant in normal subjects; one hospitalized but otherwise normal subject who was examined 15 times in a period of a year showed an extreme range of 113 to 137 cc/min. with a mean value of 122 cc.[1935]

The average rate of filtration in man corrected to standard surface area (1.73 sq. m.) * is 127 cc/min. (ch. XVII). Out of this 127 cc. of filtrate a large fraction (some 85 per cent) of the water is normally reabsorbed by a passive process in the proximal tubule (obligatory reabsorption), leaving only a small, variable quantity (some 15 per cent or 20 cc/min.) to be excreted as urine during maximal water diuresis (facultative reabsorption). In the absence of excessive hydration, most of this facultative water is reabsorbed, reducing the urine flow to (on the average) 1.0 cc/min. During extreme dehydration, complete reabsorption of water (anuria) is prevented by the osmotic activity of non-reabsorbed solutes contained in the urine.

The two human kidneys on the average contain nearly 2,000,000 glomeruli (ch XVII),[2114] each having an average volume of 0 0042 cu. mm It follows that, in each glomerulus, about 0.001 cu. mm. of filtrate is formed per second, or 25 per cent of the volume of the glomerulus. This is close to the upper limit of the rate of filtration in the capsule of the frog, as observed by the micro-collection method.[1718] If we take 1200 cc/min. as the blood flow through the two kidneys, 0 01 cu. mm. of blood, or an amount about 2 5 times the volume of the glomerulus, must flow through each glomerulus per second Book[211] has calculated that the total filtration area in the two human kidneys is 0.76 sq. m. (as compared with Vimtrup's[2114] estimate of 1 56 sq. m.) or nearly half the average body surface area in man (1 73 sq. m.). Taking renal plasma flow as 655 cc/min., some 12 cc. of plasma are circulated per second over a filter that has a surface area of 0.76 sq. m, giving a layer of plasma virtually 0 015 mm deep. It is not diffi-

* The average surface area of men and women of 25 years of age For discussion of this correction, see chapter XVII

cult to imagine that, under an effective pressure of 20 mm. Hg, 2 cc. of water could be filtered through this large expanse of endothelium per second. It amounts to no more than 1 drop per second through a membrane 8 x 8 cm. Using the above figures and taking 300 gm. as the weight of the two kidneys, the rate *of filtration per gm. of tissue is only some* 200 times the rate of filtration per unit of differential pressure in the perfused hindlimbs of cats and dogs.[1674] Taking the total glomerular volume in the two kidneys as 8.4 cc., the rate of filtration (2 cc/sec.) is about one-fourth of this volume per second.

The indirection of the filtration-reabsorption mechanism has some rather surprising consequences. At the rate of 130 cc/min., 187 liters of water are filtered from the plasma per day, which is over 50 times the volume of plasma in the body, or 15 times the volume of extracellular fluid. From this quantity of filtrate the *renal tubules must reabsorb 185.5 liters of water and something* like 1100 gm. of sodium chloride, 425 gm. of sodium bicarbonate, and 150 gm. of glucose, not to mention considerable quantities of phosphate, amino acids, vitamins, etc., in order to excrete a meager total of 60 gm. of urea and other waste products in 1.5 *liters of urine. The total work done by the kidney is roughly* proportional to the quantity of fluid reabsorbed; if no reabsorption occurred, i e. if 187 liters of glomerular filtrate were excreted per day, the kidney would be required to do no work at all; all the energy would be supplied by the heart in effecting the separation of the 187 liters of filtrate against the osmotic pressure of the plasma proteins and in pumping it against the viscous resistance through the glomerular membranes and down the tubules into the bladder. The lower the urine flow and the more differentiated the urine, the greater is the work the kidney has to perform.

PERFUSION EXPERIMENTS

Attempts to verify and explore the Ludwig-Cushny theory have until recent years taken the form of perfusion experiments using the Starling heart-lung preparation or some modification thereof. Many factors, and chiefly vasoconstrictor substances, such as serotonin,[1662] appearing in shed blood *complicate such experiments*, and since the literature has been extensively covered by Marshall [1390] and Winton,[2348] it will not be reviewed here.

SINGLE INJECTION TECHNIQUE

SINGLE INJECTION TECHNIQUE

Numerous attempts have been made to avoid the use of intravenous infusions in clearance methods in man for keeping the plasma level of various substances constant. These attempts involve either single intravenous, intramuscular, or subcutaneous injections, or combinations thereof. Certain underlying assumptions can conveniently be analyzed here.

If V, the volume of distribution of a substance (i.e the extracellular fluid), is constant, and (b) if it is assumed that mixing throughout this fluid is instantaneous so that the concentration of the substance throughout this volume is uniform, and (c) if the substance is cleared from the plasma at a constant rate, C (in cc of plasma per minute), then the plasma concentration P_2, at any time t (in minutes) after P_1, will be

$$\log P_2 = \log P_1 - \frac{Ct}{V}$$

Thus the logarithm of the plasma concentration will give a straight line when plotted against elapsed time The slope of this line, S, is the fraction of V that is cleared per minute·

$$S = \frac{C}{V} = \frac{\log P_1 - \log P_2}{t}$$

and the rate of clearance, C, is

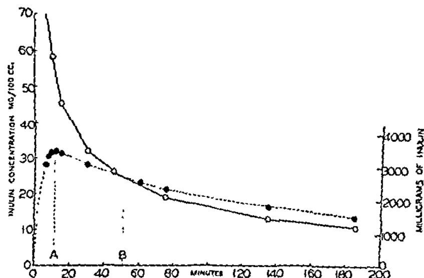
$$C = V\left(\frac{\log P_1 - \log P_2}{t}\right)$$

Under the three assumptions above, and further (d) assuming or estimating by an approximation method the volume of distribution, V, it is possible in theory to calculate the filtration rate or renal plasma flow from the rate of change of the plasma concentration after a single injection of inulin, mannitol, PAH, etc Most, if not all of these assumptions, are involved in efforts to replace the infusion method by single injection methods[47, 287, 849, 651, 664, 893, 1001, 1024, 1038, 1082, 1083, 1207, 1513, 1518, 1685, 1735, 1736, 2037]

Significant errors, however, are introduced in clearance determinations by any method where the plasma concentration of the reference substance is changing rapidly because one or more of the assumptions stated above is not valid.

a. *Volume of distribution* The volume of distribution of a substance cannot be assumed to be constant in any two normal subjects, whether this substance is confined to the extracellular fluid (inulin) or whether it penetrates tissues to some extent (PAH) Much less can this assump-

tion be made in subjects with disturbed renal function, where there is the greatest need for accurate renal function studies. Neither can the volume of distribution of any substance be calculated by extrapolation from the falling plasma concentration after a single intravenous injection.



fluid concentration reverses at A, in 3 men this occurred at 5, 12, and 22.5 min., and in 2 dogs at 7.5 and 10 min after injection. Identity of concentration is reached only at B, which occurred at 9, 33, and 51 min. in the 3 men, and at 14 5 and 25 min. in the 2 dogs. (Schachter, Freinkel, and Schwartz[1773])

Schachter, Freinkel, and Schwartz[1773] have treated the theoretical aspects of mixing between the plasma and extracellular fluid, and they have shown, as would be predicted in theory, that after a single injection the mean concentration of inulin in the extracellular fluid is identical with that in plasma at only one moment, as shown in figure 10. At all other times a concentration gradient exists, first from plasma to extracellular fluid, and then in the reverse direction. That the distribution of inulin is far from uniform after a single injection is also demonstrated by Gaudino's studies on the kinetics of distribution.[743] Because of this fact, the single injection method cannot be used to determine the extracellular fluid volume, all other assumptions being valid. The only appar-

ently reliable method of measuring the extracellular volume is the constant intravenous infusion-equilibration method.[751, 1808 1811]

Schachter, Freinkel, and Schwartz,[1771] and Robson, Ferguson, Olbrich, and Stewart[1735] have pointed out that, after a single intravenous injection of inulin, equilibrium between the plasma and extravascular component of the volume of distribution is never reached, and consequently the falling plasma inulin concentration is not exponentially related to time. Robson *et al* have devised a formula that incorporates functions demanded by the failure of equilibration and applied it to the determination of clearances by the single injection method, comparing the results with the standard clearance technique Venous blood was used, but the authors do not discuss errors arising from inulin arterial-venous differences Moreover, they have chosen, whether necessarily or not, to use a single urine collection period extending from 35 to 120 min. after the injection of inulin In this form, the method is not adapted to the examination of rapid changes in the filtration rate, nor is it adapted to the circumstances where the extracellular fluid volume is shifting, and it is questionably adapted to states such as hydronephrosis where the dead space is large, or to circulatory failure or edema where mixing of inulin with the interstitial fluid is greatly prolonged No error is introduced in any of these circumstances when a constant plasma level is used.

b *Uniform distribution* The analytical sample must be obtained from arterial or systemic venous blood Storage of the reference substance in the tissues or interstitial fluid of the arm will afford a depot that will tend to retard the decrement in systemic venous concentration and to raise this figure to levels above the concentration of arterial blood that perfuses the kidney, giving rise to a significant arterial-venous difference. The systemic venous blood will tend to have an erroneously high concentration on falling plasma curves and to give erroneously low clearances.

The arterial blood supplying the kidneys is presumably identical in composition with the mixed venous blood in the right heart, but the mixed venous blood differs from the systemic venous blood (ex antecubital vein) because of dilution of the mixed venous blood by renal venous blood (*c* 20 per cent of the total) from which the reference substance has in part (inulin) or wholly (diodrast, PAH) been removed. Relative to the error from dilution of the systemic venous blood by renal venous blood, it may be argued that the circulation time from brachial artery to antecubital vein is so short (less than 1 min) that, apart from the storage effect noted above, the concentration in the antecubital vein may be considered identical with that in the brachial

and therefore the renal artery. In evaluating these factors, the relative circulation time from brachial artery to antecubital vein, and, alternatively, from antecubital vein to the right ventricle, must be weighed. They are both short and probably about the same length. Were the systemic blood diluted with renal venous blood by 20 per cent in the interval required for the total blood volume to be circulated once around the body, or about 1 min, the concentration of diodrast or PAH should decrease at a rate of 20 per cent per minute. The observed decrease is much slower (about 1 per cent per minute), presumably because the interstitial fluid, which has a volume some 2.5 to 3.0 times the plasma, the red cells, and other tissue reservoirs are constantly supplying solute to maintain the systemic plasma concentration. The true arterial-venous difference will therefore lie somewhere between the extremes indicated by each process separately Brun, Hilden, and Raaschou[277] have discussed these sources of error and find that the venous blood was actually 28.7 per cent higher in diodrast and 7.4 per cent higher in inulin than simultaneous arterial blood. On a rising plasma curve the errors will be of the same magnitude but opposite in direction, and the calculated clearances will be erroneously high

This source of error can be avoided by using arterial blood or by maintaining the plasma level constant by continuous infusion; in either case the concentration in arterial and mixed venous blood will be identical because the latter is receiving solute at a rate equal to that at which it is being excreted by the kidneys.

c *Constant clearance* into the bladder implies an accurate knowledge of the mean concentration in the plasma from which a given urine sample is formed A significant interval is required for the urine to pass down the tubules, collecting ducts, and ureters before it reaches the bladder. Goldring *et al.*[197] originally estimated this interval (including circulation time from the antecubital vein) by determining the 'first appearance' time of phenol red at various urine flows, and arrived at the mean figure of 2.5 min.; they therefore recommended that the plasma concentration be read back 2.5 min from the middle of the urine collection period, using semi-logarithmic graph paper for the interpolation of P. They recognized that this delay time would vary with the urine flow and might be considerably larger during oliguria, but their investigations were chiefly concerned with urine flows of 1 to 5 cc/min. The dead space in a single dog kidney is about 6 cc.; if this dead space is washed out by new urine moving in a solid front against old urine, the delay time should be 1 min at a flow of 6 cc/min, 6 min. at a flow of 1 cc/min, 12 min. at a flow of 0.5 cc/min., etc. Such is apparently not the case, however.

Michie and Michie[1446] have shown by ureteral catheterization in man that, in the normal kidney, after the nearly instantaneous establishment of the plasma level and at urine flows of 1 to 4 cc/min per kidney, some 20 to 30 min. are required before the urine *comes into equilibrium* with the plasma in the excretion of inulin, mannitol, thiosulphate, PAH, and phenol red; they conclude that the equilibrium time is prolonged to this extent because of the mixing of old and new urine This delay, interval, which is 10 times the minimal appearance time, is independent of whether venous or arterial blood is used. The error from this source will increase greatly at low urine flows.* An analysis of dead space error has recently been made by Bojesen,[204] who finds that the volume of the renal pelvis in the dog increases with urine flow, while Morales, Crowder, Fishman, Maxwell, and Gomez[1474a] have adduced functional evidence that the volume of the tubules increases with diuresis. The net effect is to keep the first appearance time constant regardless of urine flow. These authors point out that in theory an equilibration time of some 25 minutes in man, as recorded by Michie and Michie, is compatible with a first appearance time of 150 seconds.

It has been the experience of workers in the writer's laboratory that an abrupt decrease in urine flow is usually accompanied by a transitory and apparently false drop in all clearances, as though the volume of the dead space has been abruptly increased A suspicious increase in all clearances is similarly associated with sudden increases in urine flow. The explanation of this phenomenon is obscure, but it seems probable that the error, if real, will be exaggerated when it is necessary to extrapolate back in time to correct for delay time with falling plasma levels. Brun *et al* also recognize the possibility of error on falling plasma curves if diodrast or PAH accumulates in the renal tissue (or interstitial fluid) before excretion

In view of these sources of error, it is believed that the use of changing plasma concentrations for the measurement of clearances, and particularly of diodrast and PAH, is precarious. There are many sources of error in the clearance technique that cannot be so easily avoided, and it seems unwise to compound them unnecessarily. The introduction of a satisfactory constant infusion pump[1904] and of flexible, intravenous retention catheters[650 1187] affords methods of maintaining constant plasma levels of all test substances for long periods and for observations on patients during exercise, etc. For all purposes they are an improve-

* Brun, Hilden, and Raaschou,[278] from a study of the rate of excretion of thiosulphate after establishment of a constant plasma level in man, arrive at a mean figure of 5 min for urine flows of 2 to 5 cc/min.

ment upon the Murphy drip, the Shannon tunnel clamp,[228] and the intravenous retention needle, but this simple equipment is available in every ward and is adequate for most clinical purposes.

THE CONSTANT INTRAVENOUS INFUSION TECHNIQUE

For any exogenous substance that is not metabolized, stored, or excreted otherwise than in the urine, the rate of excretion (UV) must be equal to the rate of infusion (IV) under conditions where the plasma concentration and the volume of distribution are constant. The steady state, as indicated roughly by a constant plasma concentration, may be designated 'infusion equilibrium' Berger, Farber, and Earle [124] have utilized this principle to determine the filtration and renal blood flow without the collection of urine. The rate of infusion, IV (where I is the concentration in mg/cc. in infusion fluid and V is the rate of infusion in cc/min.), is substituted for the rate of excretion, UV, in the clearance calculation, i.e. $IV/P = UV/P$. In practice, the infusion must be maintained at a very accurate rate until infusion equilibrium is reached and before it can be assumed that $IV = UV$ If P continues to change, appropriate correction must be made in the UV term for storage or discharge of inulin in the extracellular space.

Berger *et al.* report good agreement between bladder clearances and clearances calculated by the constant intravenous infusion technique in normal subjects, and fair agreement during acute changes in filtration rate and renal plasma flow. Unsuccessful attempts to use the infusion technique resulted from failure to attain equilibrium between IV and UV, especially in the presence of edema, and they note that this technique may be erroneous in short experiments in subjects whose clearances are less than 60 per cent of normal.

The technique is sound in principle, but the investigator should satisfy himself of his competence to check bladder clearances by this method Workers in the writer's laboratory have been rather disappointed in this respect and have not substituted the infusion technique for bladder clearances in any important study, even in those extending over periods of 24 hr. where it would be most useful It seems probable that, as Landowne and Alving [1207] note, a prolonged period of time is required for a change in renal function to be reflected in significant changes in plasma concentration. This will be more important with PAH, which penetrates some tissues,[88, 1808] than with inulin, which is distributed only in the extracellular fluid; [749 1809, 1811] but even with inulin there is relatively slow mixing in the extracellular fluid [749] and opportunity for large errors.

CHAPTER IV

Excretion of Urea

HISTORICAL NOTE

Of all substances in the urine, urea has been of the greatest interest to both the physiologist and the clinician. It is the chief nitrogenous end product of the combustion of protein and, apart from water, the chief constituent of the urine Because the urea clearance is one of the most widely used indices in the evaluation of renal disease, the physiological factors involved in its excretion are of considerable importance.

Urea was first prepared by Rouelle in 1773 by the alcoholic extraction of evaporated human urine. This investigator was also one of the first to extend biochemical investigations to the lower animals, for he demonstrated that urea is present in the urine of the camel, horse, and cow. In the hands of Scheele, Proust, Fourcroy, and others, the separation and identification of the nitrogenous constituents of urine progressed rapidly in the early years of the nineteenth century, and *urée*, as it was named by Fourcroy to avoid confusion with *urique* (uric acid), received its full share of attention Of urea Fourcroy wrote in 1804, '. . . its expulsion is the principal, and, the most necessary, the most remarkable purpose of the urinary evacuation ' This is forgivable overemphasis: urea is the most abundant compound in the urine, being the chief non-volatile product of metabolism, but it is

almost non-toxic and from a functional point of view it is one of the least important constituents in the urine.

It was only a few years after Prout had established its empirical formula that Wöhler in 1828 demonstrated that this 'organic' compound could be prepared artificially from ammonium cyanate. The effect of this discovery upon the science of the past century cannot be overestimated, for it constituted one of the first and also one of the most effective blows delivered against the doctrines of vitalism, which had dominated natural philosophy up to the nineteenth century. It was owing less to coincidence than to the fact that chemistry and medicine were developing hand in hand that, in the year before Wöhler's work, Richard Bright first described the disease which is named after him. It was known that urea was present in the blood, that there was a deficiency of urea in the urine of dropsical patients, that dropsy is frequently associated with albuminuria and at times with diseased kidneys. But it was Bright's achievement to demonstrate the accumulation of excess urea in the blood in dropsy, and to correlate this circumstance with its decreased concentration in the urine, with albuminuria, and with diseased kidneys. When, in 1842, Dumas and Cahours showed that urea was a product of the combustion of protein food (the essential principles of metabolism having been formulated by Lavoisier a generation before), the naturalistic description of renal disease was complete.

The term 'uremia' early became associated with renal insufficiency. It is now thought that few if any of the clinical signs and pathological changes associated with renal insufficiency are due specifically to the accumulation of urea in the body, for urea is one of the least toxic of all nitrogenous compounds; but this in no way diminishes the importance of the fact that the capacity of the kidney to excrete it constitutes a valuable test of renal function.

Strauss in 1903 and Urdal and Javal in 1904 introduced into clinical medicine the determination of blood urea as a diagnostic test; during the next two decades, aided chiefly by the biochemical methods developed by Folin, this determination was supplemented by the determination of the non-protein nitrogen, creatinine, and uric acid content, since all these tend to rise above

normal values in advanced renal disease. In no case, however, is the plasma concentration of any compound a reliable index of renal function, since it varies also with the rate of production; and, in the case of urea, the rate of excretion and hence the plasma concentration depend on the rate of urine flow. Some investigators emphasized the urea content of the urine under more or less constant conditions, while others believed that the degree to which urea could be concentrated (i.e the U/P ratio) constituted a better functional test. By modern standards, all of these tests have proved to be of little physiological value.

It was not until 1912 that Ambard and Weill attempted to evaluate renal activity by what we may call a 'dynamic' test, i.e. one that relates the quantity of urea excreted per unit time to the quantity in each cc. of plasma.* Ambard and Weill arrived at an empirical equation which, though it described the facts fairly well at low urine flows, was difficult to interpret physiologically.†

A little later some degree of simplification in this problem was effected in the demonstration by Marshall and Davis in the dog and Addis in the rabbit that the rate of urea excretion (UV) is directly proportional to the blood urea content (B), providing the urine flow is fairly large. It is this fact that constitutes the central principle of the Addis 'urea excretion ratio,' according to which the quantity of urea excreted per unit time (1 hr.) (UV) divided by the concentration in the blood (B) is constant for any one individual under 'standard conditions.' ‡ § But the Addis

* For a fuller discussion of the history of this problem the reader is referred to Smith[1511]

† With numerical constants omitted, this equation is $K = \frac{B}{\sqrt{D}\sqrt{U}}$, where B and U are the concentrations of urea in the blood and urine respectively, and D is the rate of urea excretion. The relationship of Ambard's formula to the standard urea clearance is discussed by Peters and Van Slyke[1157]

‡ The Addis excretion ratio is an hourly rather than a per minute clearance at maximal urine flows

§ In 1928, Addis[10] wrote 'Part of the function of the kidney consists in moving urea from the blood into the urine Now, regardless of the mechanism by which this is accomplished, we may conceive the blood passing through the kidney as consisting of 2 portions, a portion which passes through unchanged and another portion from which the urea is completely removed The volume of this urea-free part of the blood can be determined (by UV/B) ' In a footnote

excretion ratio had limited applicability, since the 'standard conditions' required maximal diuresis or, at least, a very large urine flow, a condition not always realizable in disease.*

STANDARD AND MAXIMAL UREA CLEARANCES

In 1921 Austin, Stillman, and Van Slyke [65] re-examined the influence of urine flow on the excretion of urea in man and found that the expression UV/B (they preferred 1 min. rather than 1 hr. as their unit of time) is constant in any one individual so long as the urine flow exceeds an 'augmentation limit,' which is usually about 2.0 cc. per 1.73 sq. m. of body surface area. When the urine flow fell below this limit, the urea clearance fell with the urine flow, the clearance then becoming proportional approximately to the square root of the flow; i.e. the equation must be written $(UV/B) \times 1/\sqrt{V} = K$. This is equivalent to writing $U\sqrt{V}/B = K$. It was in a subsequent extension of this work that Möller, McIntosh, and Van Slyke [148] applied the term 'clearance'; the expression UV/B they called the 'maximum' clearance, and $U\sqrt{V}/B$ they called the 'standard' clearance.†

at this point he adds, 'I am indebted to my colleague, Prof. G. D. Barnett, for this conception of the meaning of the ratio He pointed out, soon after publication of the paper on the ratio as a method for determining the amount of renal tissue [here Addis refers to a paper published in 1917], that it was only through recognizing that the ratio was the volume of blood freed from urea that it could be thought of as a concrete and reasonable measure of function.'

It is difficult to judge the importance of words as the vehicles of ideas, but one may venture to suggest that had Barnett or Addis used Van Slyke's happy expression 'cleared' instead of 'freed,' renal physiology might have been significantly catalyzed in 1917 or thereabouts ('freeance' would be a more terrible word than 'clearance'). However, he anticipates having to defend this position against those who do not like the word 'clearance' as well as he does

* It is unfortunate that most of the careful studies carried out by Addis and his coworkers were made on the rabbit this animal is unique, as compared with the dog and man, in that it is readily excited, and during excitement renal vasoconstriction reduces the filtration rate and, of course, the excretion of urea (ch xvii).

† The use of the term 'standard clearance' to define the empirical expression $U\sqrt{V}/B$, was perhaps unfortunate, as was the introduction of the square root radical. The demonstration of the constancy of the urea clearance (UV/B) at urine flows above 2 cc/min. and the introduction of the term 'clearance' itself have been of inestimable value to renal physiology. But, paradoxically, Möller, McIntosh, and Van Slyke confused rather than clarified the problem by calling

In these calculations V is corrected to a body surface area of 1 73 sq. m (as representing the average surface area of adults; see p. 543). The 'maximum clearance' has an average value of 75 cc/min., and the 'standard clearance' an average value of 54 cc/min, of *whole* blood. It is conventional to divide the observed clearances by 75 or 54, depending on V, and to multiply by 100, and thus express the results as per cent of normal.

Chesley [366] has studied the urea clearance at very low urine flows and finds that, at flows below 0 35 cc/min, the U/B ratio becomes constant in any one individual, so that the clearance UV/B varies in direct proportion to V He suggests that, at flows below 0 35 cc/min., a 'minimal' clearance be calculated by multiplying the observed U/B ratio by 0 35, disregarding the actual urine flow. To calculate the clearance as per cent of normal, the observed U/B ratio should be divided by the 'normal' ratio, 91 5, and multiplied by 100, or simply multiplied by 1 11

In recent papers Bing [168] and Williams [2222] have proposed formulae which they believe to be more accurate than the 'standard' and 'maximal' clearance equations of Moller, McIntosh, and Van Slyke. The essential point is, how accurately does any formula permit one to calculate, from clearances determined in a subject at widely differing urine flows, the clearance that he would show at a given urine flow. Van Slyke [2091] has analyzed the formulae proposed by Bing and Williams and shown that in this sense they are less accurate than the widely used 'standard' and 'maximal' clearance calculation The results confirm Dole's [540] conclusion with regard to the clinical use of urea clearance formulae, that 'the "maximal" and "standard" urea clearance formulae are adequate for their purposes, except for conditions of unusually small urine flows.'

Dominguez [532] collected from the literature data on urea clearances in the dog and, adding further observations furnished by Goldblatt, formulated an equation to describe changes in the urea clearances relative to the rate of urine flow More recently, Dominguez and Pomerene [533] have extended this analysis to man In both instances the equations are empirical and neglect variations in the urea clearance which are demon-

$U\sqrt{V}/B$ a 'clearance', it does not signify a virtual volume of cleared blood, but is instead the product of a mathematical operation in which a (true) clearance, UV/B, is multiplied empirically by $\sqrt{V}$, hence it is only a presumed clearance, predicated on the assumption that below 2 cc/min UV/B will decrease in proportion to $\sqrt{V}$, and calculated for convenience to the value of $V = 1\ 0$

strably attributable to changes in the filtration rate. To meet this obvious physiological requirement, it is necessary to treat not the absolute urea clearance but the urea/inulin clearance ratio. Moreover, it is desirable in such analyses to take into account the known—however poorly known- [illegible]
by extr [illegible]
tion of [illegible]
(*vide infra*) points out, as the urine flow approaches zero the time available for diffusion becomes indefinitely prolonged and it would seem more reasonable to expect equilibration between urine and blood (i.e. a U/P ratio of 1.0) unless urea is actively secreted.

The 'maximal' (or true) clearance, UV/B, bears a simple physiological relationship to the rate of glomerular filtration and urine flow, and for physiological analysis this is the only calculation that is useful. Furthermore, the clearance should be calculated as a plasma clearance (UV/P) rather than as a whole blood clearance (UV/B). Urea is excreted only by filtration, and the filtration of plasma water causes only an insignificant change in the water content of the red cells (because of a change in oncotic pressure); therefore, the concentration of urea in the red cells undergoes no change during passage through the glomeruli. The use of whole blood concentrations leads to error because of the difference in water content and therefore urea content of the red cells, an error which will vary with the hematocrit. Only the plasma urea clearance can be compared with the inulin or other clearances, which involve only clearance from the plasma.

MECHANISM OF UREA EXCRETION

The plasma urea clearance represents the volume of plasma nominally completely cleared of urea in 1 minute's time; or, alternatively, the volume of plasma required to supply the urea excreted in 1 minute's time.

The urea clearance ranges from 30 to 60 per cent of the inulin clearance, depending on the urine flow. Urea is completely filtrable, and there is as yet no evidence that it is destroyed in the tubular urine, so we must interpret the deficit in the urea clearance below the filtration rate as indicating that a considerable fraction of the filtered urea diffuses back through the tubules.

This back diffusion is readily understood in light of the fact that urea is one of the most diffusable organic compounds known (as it would have to be to escape from the tissues in which it is formed by metabolism) and that when administered it is distributed, as first shown by Marshall, throughout the body water.

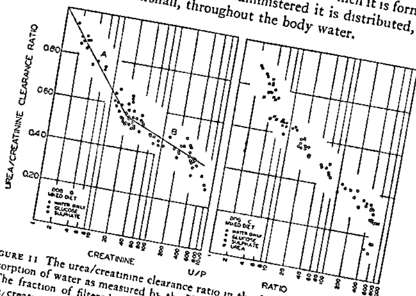


FIGURE 11 The urea/creatinine clearance ratio in the dog in relation to the reabsorption of water as measured by the U/P ratio of creatinine

The fraction of filtered urea that is reabsorbed is equal to 1.0 minus the urea/creatinine clearance ratio (left) The open circles represent observations at normal urine flows and during water diuresis, the closed circles observations made during osmotic diuresis with glucose, sulphate, or urea

It is suggested that line A represents 1 reabsorptive process related to the obligatory reabsorption of water in the proximal (and thin) segment, and line B a second reabsorptive process related to the facultative reabsorption of water in the distal system The first process cannot be abolished in the normal kidney by water diuresis, which reduces the creatinine U/P ratio to 6 or 8 as a minimum (Shannon [illegible])

The urea/inulin (or, in the dog, creatinine) clearance ratio reveals the fraction of filtered urea that is excreted, and hence 1.0-urea/inulin (or creatinine) clearance ratio gives the fraction of urea that has been reabsorbed As the urine flow decreases, the urea/inulin clearance ratio decreases, indicating that the amount of urea reabsorbed increases as the urine moves down the tubules and becomes more concentrated (figs 11 and 12). *A priori*, one

might attribute the reabsorption of urea at all urine flows to a unitary process related to the rate of urine formation; but the evidence indicates that at least two processes are involved, one of which (proximal reabsorption) accounts for the deficit of about 40 per cent at high urine flows (12 cc/min. or above in man) and a second process (distal reabsorption) that becomes significant at lower flows and accounts for the increasing deficit in the urea clearance as the urine flow falls to very low values.

The most extensive study of this problem is that of Shannon,[1850,1854] who has shown that the urea/inulin clearance ratio in the dog increases systematically with the urine flow throughout the entire range of the latter. No point may properly be designated as an 'augmentation' limit, in the conventional sense. The rate at which the clearance ratio changes is quantitatively not the same in all animals, or necessarily the same under all conditions, and one animal must be examined at all possible rates of urine flow in order to disclose the fundamental relationships.* The degree to which the urine has been concentrated by the reabsorption of water is indicated by the inulin (or creatinine) U/P ratio. The relation between urea reabsorption and water excretion is therefore best portrayed by plotting the clearance ratio against the inulin or creatinine U/P ratio, using the logarithm of the latter for convenience, since this term varies from 2 to nearly 600.

Data from 2 dogs are presented in figure 11. The open circles (curve B) represent observations made throughout the entire normal range of urine flow, i.e. between the extremes of water deprivation and water diuresis. During water deprivation the creatinine U/P ratio reaches its maximal value of 600 or more,

* One complicating factor is that during the period when the urine flow is increasing, as during the ascending limb of water diuresis, the excretion of urea is anomalously increased; to obtain reproducible results it is necessary to make observations either during a constant urine flow or on the descending limb of water diuresis. A second complicating factor is that the urea clearance is excessively depressed, relative to the filtration rate, when the urine flow is very low. The explanation of these phenomena is unknown, except that the first is not related to the degree of hydration of the body or presumably of the tubule cells. It appears to be related to an abrupt change in the rate of water reabsorption (or excretion) considered mechanically. Neither phenomenon is explicable in terms of dead space error

where 599/600 of the water of the glomerular filtrate has been reabsorbed. During water diuresis, the lowest creatinine U/P ratio reached in these dogs was about 15, when 14/15 of the water had been reabsorbed.* (This minimal limit of water reabsorption represents approximately the complete cessation of water reabsorption by the distal tubule.)

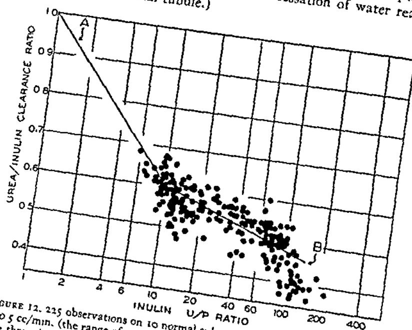


FIGURE 12. 225 observations on 10 normal subjects at urine flows from 20 down to 0.5 cc/min. (the range of normal diuresis) Line B the best free-hand straight line through these data Line A, the relationship to be expected at inulin U/P ratios below 8 (osmotic diuresis), based on observations on the dog (Chasis and Smith [86])

The other symbols (A) in figure 11 represent observations made during forced (osmotic) diuresis induced by the intravenous infusion of glucose, sodium sulphate, or urea itself Here the osmotic pressure of the infused solute retards passive water reabsorption in the proximal tubule and makes it possible to reduce the minimal creatinine U/P ratio to about 2.0, where only 50 per cent of the water of the glomerular filtrate is reabsorbed.

* This minimal U/P ratio varies in different individuals. The figure 8 is more nearly representative of both dog and man during maximal water diuresis.

The fact that line A extrapolates to a urea/creatinine clearance ratio of 1.0 when the creatinine U/P ratio is 1.0 indicates that there is no active reabsorption of urea.* Throughout the entire range of urine flow it is permissible to interpret the deficit in urea clearance as the result of passive diffusion of urea,† somehow related to the degree of concentration of the tubular urine ‡ and hence to the diffusion gradient of urea between the tubular urine and the blood and the time available for diffusion.

The fact that the data divide themselves into two rectilinear or nearly rectilinear phases indicates that two processes are involved; one process is operative at creatinine U/P ratios from 1.0 to 10 or 15, and a second at creatinine U/P ratios from 10 or 15 up to 800.

Phase A in urea reabsorption is identified by Shannon with water reabsorption in the proximal tubule; here about 40 per cent of the urea originally contained in the glomerular filtrate diffuses back into the blood in consequence of the progressive concentration of the tubular urine in the proximal tubule from a creatinine U/P ratio of 1.0 to a U/P ratio of 8. Phase B is identified with water reabsorption in the distal tubule, where further water reabsorption raises the creatinine U/P ratio to very high values. Since phase A is invariably completed at the highest urine flow obtainable during water diuresis, phase B invariably begins with a urine from which some 40 per cent of the filtered urea has already been reabsorbed. It may be inferred from the steeper slope of line A that the proximal tubule is more permeable to urea than is the distal tubule.§

* Schou[1799] has shown that, during extreme sulphate diuresis in the rabbit, the urea U/P ratio approaches that of creatinine It is never more.

† That urea is reabsorbed by passive diffusion was first suggested by Rehberg,[1688,1689] Poulsson,[1555] and Holten and Rehberg[1030] from urea/creatinine clearance ratios in man

‡ The degree of urea reabsorption at a given creatinine U/P ratio in a given dog is quantitatively the same when the filtration rate is high (on a high protein diet) and when the filtration rate is low (on a low protein diet).

§ It was the behavior of the urea/creatinine clearance ratio at varying creatinine U/P ratios, as shown in figure 11, together with the minimal U/P ratio attained during water diuresis and in diabetes insipidus, that first led the writer to postulate the existence of two modes of water reabsorption, 'obligatory' (proximal) and 'facultative' (distal)[1925]

The relation between urea reabsorption and water reabsorption in man is quite similar to what is observed in the dog. No data are available on the urea/inulin clearance ratio during osmotic diuresis, but the data in figure 12 show that there is a progressive reduction in this ratio between inulin U/P ratios of 8 and 200.* At a U/P ratio of 8, approximately 40 per cent of the filtered urea is reabsorbed, as in the dog.

BACK DIFFUSION OF UREA

The back diffusion of urea has been treated mathematically by Dole [530] under certain simplifying assumptions, and in terms of Fisk's law of diffusion Dole accepts that in man 57 per cent and in the dog 68 per cent of the filtered urea has been reabsorbed in the proximal tubule in consequence of the passive reabsorption of water, and therefore that these fractions represent the asymptote which is approached by the urea/inulin (or urea/creatinine) clearance ratio at high urine flows. His mathematical analysis is therefore confined, in the first instance, to the effects of urine volume on reabsorption in the distal tubule He further assumes that urea is reabsorbed after water is reabsorbed, and makes no allowance for urea reabsorption concurrent with water reabsorption These assumptions may not be exact, but the error entailed is probably too small to be significant.

Dole's analysis leads to the equation

$$C_U = C_F \times e^{-\left[\frac{k_1}{V}\left(\frac{\log C_F/V'}{C_F/V' - 1}\right) + \frac{k_2}{V}\right]}$$

where C_U is the urea clearance, C_F the inulin clearance in man or the creatinine clearance in the dog, e the base of natural logarithms, k_1 a constant involving the tubular area through which reabsorption is occurring, V' the urine flow nominally at the end of the proximal tubule, k_2 a constant involving the permeability of the tubules, and V the bladder urine flow. The constant k_2 can be determined by graphic analysis of C_U/C_F and $1/V$.

All variables in this equation are subject to measurement except V', and Dole assumes this to be relatively constant under normal conditions

*The urea/inulin clearance ratio has not been examined in man at urine flows below 0 35 cc/min (Chesley's 'minimal' clearance range) His data on urea excretion in normal subjects were derived from routine renal function tests but may represent anomalous circumstances in which the filtration rate was subnormal.

in normal subjects, so that when filtration is approximately constant the first term of the exponent may be grouped into a single constant, ϕ. Then

$$C_U = C_F \times \phi \times e^{-k_1/V}$$

The factor ϕ, which represents the fraction of urea escaping reabsorption in the proximal tubules, has a value of about 0.6 in man. The product

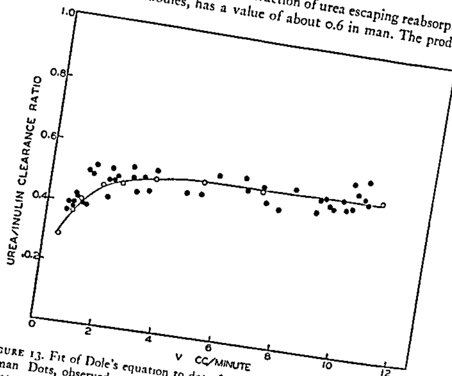


FIGURE 13. Fit of Dole's equation to data from Chasis and Smith on 1 normal human Dots, observed ratios on falling flows, circles, theoretical points from equation

(Dole ***) $$\frac{C_U}{C_F} = 0.57e^{-\frac{0.36}{V}}$$

$F \times \phi$ gives the maximal value of the urea clearance toward which the observed urea clearance approaches when the urine flow is large

The fit of the theoretical equation to data obtained during decreasing urine flows from a normal subject is given in figure 13, and to data from a normal dog in figure 14 The equation above has the advantage of covering Chesley's minimal urea clearance at low urine flows (below 0.35 cc/min) as shown in figure 15, but this may be fortuitous In terms

of Dole's analysis, a maximal urine urea concentration is to be expected at *urine flows somewhere between 0.15 and 0.30 cc/min in man.* Owing to the technical difficulties of obtaining extremely low urine flows, and because of probable changes in filtration rate and proximal water reabsorption in oliguria, it is not feasible to make a test of the prediction

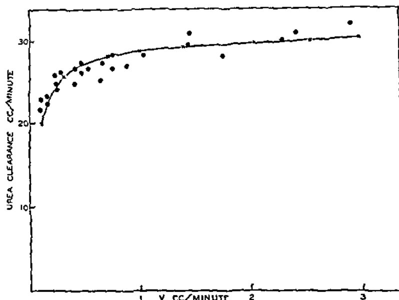


FIGURE 14 Fit of Dole's equation to the excretion of urea in 1 dog studied by Shannon Dots, observed values, crosses, values calculated from the equation

$$C_U = 30e^{-\frac{0.042}{V}}$$

(Dole [120])

that a maximal concentration of urea in the urine will be reached before the urine flow approaches zero

Dole points out that the dog has not only smaller tubules, but a smaller *number of nephrons, and hence the surface area available for back* diffusion is less than in man If the permeability of the tubules in the two species is of the same order, the exponent of the diffusion equation should be about *one-fifth to one-tenth that found in man.* This is found to be so, as is shown in figures 13 and 14

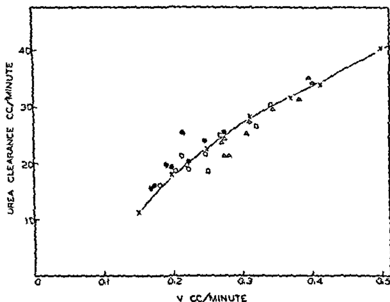
The virtual permeability of the distal tubules in man is estimated to be of the order of 10^{-5} cm/min, which is to be *compared with* 10^{-2}

cm/min. for the ox erythrocyte Obviously the permeability of the tubule wall to urea is of a low order.

During osmotic diuresis induced by urea in dogs, Mudge, Foulks, and Gilman [1458] find that the relative excretion of urea and water increase concomitantly so long as the filtration rate is maintained; but if the filtration rate decreases, the urea/creatinine clearance ratio decreases out of proportion to the decrease in the creatinine U/P ratio. The authors attribute the increased reabsorption of urea under these circumstances to an increase in the time of exposure of the tubular urine, which permits relatively more urea to diffuse out of the urine. A similar phenomenon is reported in man where the filtration rate is reduced (chs. xx and xxi).

Holden and Bulger [1026] have examined the relation between urine flow and the clearances of urea, sucrose, exogenous and endogenous creatinine, uric acid, amino acid nitrogen, inulin, sulfadiazine, and sulfathiazole on one subject, dehydrated from 12 to 30 hr. Urine was collected by voiding after urine collection periods of 30 to 40 min. I their data all clearances tend to decrease during oliguria, and the urine volume-clearance relationship in each case can be represented by an exponential relationship of the type developed by Dole [830] for urea and in accordance with the diffusion coefficients of the respective substances. The authors argue that the deficit in clearance of certain substances at high urine flows (creatine, ferrocyanide, xylose, and sucrose) can be explained by diffusion, as in the case of urea This study is open to the criticisms that (a) assuming urine flows as low as 0.3 to 0 5 cc/min, the total urine volume in a 40 min. collection period would not exceed 12 to 20 cc., and no accurate clearance information could possibly be obtained on voided specimens, (b) the alleged decrease in clearances during oliguria is in some instances very slight (inulin, sucrose, exogenous and endogenous creatinine, sulfathiazole) and the purported agreement between theory and observation with respect to volume-clearance relationship carries little weight, since the exponential equation developed for urea could be 'fitted' to any such group of limited data with little deviation in the narrow range of observed points; (c) the possibility that the filtration rate decreases during dehydration is ignored, as is the fact that (at urine volumes above 1 cc/min) water diuresis is frequently accompanied by a transient increase in inulin clearance; [363,1880] and (d) the reabsorption of 26 per cent of filtered xylose cannot be attributed to diffusion since phlorizin in man and hyperglycemia in the dog abolish this deficit and bring the xylose clearance up to the inulin or creatinine clearance,[1882] while the reabsorption of 26 per cent of filtered creatine is probably not attributable to diffusion since the administra-

up to the creatinine clea... basis of argument for the back diffusion of 32 per ce... is arbitrary, the ferrocyanide and creatinine clearances in the dog are identical;[2093,2094] there is considerable question whether sucrose is re-



...on the excretion of urea to 4 normal ... measured ...d ...al

$$\frac{\quad}{C_F} = \ldots$$

If an average filtration rate of 120 cc/min. be assumed, the value C_U/C_F = 68/120 or 0.57 as in figure 13 (Dole [430])

absorbed at all in man, and the subject requires further investigation;[1102,1926,1997] (e) the data show marked differences in the alleged bac... ...of inulin and creatinine, without reference to the fact th... ...the creatinine/inulin ratio in t...

dog, even up to inulin ...

it is clear that the 'fitting' of exponential curves to the data presented by these authors cannot prove back diffusion of the substances mentioned The question of back diffusion can be answered only by examination of simultaneous clearance ratios, the best standard of reference available at present being inulin.

CLINICAL USE OF UREA CLEARANCE

No recondite analysis of the kinetics of back diffusion of urea is of much aid in the clinical problem of assessing the functional capacity of the kidneys by means of the simple urea clearance test. For this reason it is desirable at the present time to adhere to the approximate description of this process represented by the 'maximal' and (if necessary) 'standard' clearance procedures. The former is to be preferred, since the urea clearance in man changes little at urine flows above 1.5 cc/min.

As said above, for critical studies the plasma clearance should be used, but no large series of plasma urea clearances is available for statistical reference, and for clinical purposes it seems best to adhere to whole blood determinations and the signification UV/B to prevent confusion with plasma clearances (UV/P). The mean plasma clearance in 10 normal subjects studied by Smith, Goldring, and Chasis [1898] averaged 70.7 cc/min. per 1.73 sq. m. The plasma clearance calculated from the accepted normal value for the whole blood maximal clearance of 75 cc/min. per 1.73 sq. m., assuming a hematocrit of 40 per cent and 70 per cent water content in the cells, would be 67.5 cc. The average urea/inulin clearance ratio in 37 normal subjects studied by Blegen, Haugen, and Aas [193] was 0.59, and Brun, Hilden, and Raaschou (cited by Raaschou [1665]) give the average urea/inulin clearance ratio in 20 normal subjects at random urine flows as 0.65 (0.458 to 0.776), comparing this figure with that of 0.64 (0.59 to 0.67) obtained by Shannon and Smith.[1868]

The more exact interpretation of the pathological physiology of the kidney cannot rest upon the assumption that the urea clearance bears any constant relationship to the filtration rate, for urea is too diffusable and its excretion involves too many variables as judged by the inulin clearance. Indeed, it would be fortunate if a molecule even larger than inulin were available for

the measurement of the filtration rate, for use under conditions where the permeability of the tubules is possibly increased.

But the fact remains that, for ease and rapidity in assessing renal function in general ward service, the urea clearance is unequalled. More than any other single determination, it has guided clinical investigation through many phases of disease, particularly in reference to the genesis of azotemia. But, in its application, accuracy in blood and urine analysis and in urine collection remains of paramount importance.

A wealth of papers, too many to include in the present bibliography, is available on the urea clearance in a variety of physiological and disease states and reference can only be made to a few:[59, 981, 986, 1046, 1051] The following articles deal with the urea clearance in the dog:[48, 941, 1027, 1079, 1097, 1669, 1703, 1850, 2036, 2093, 2098]

The significance of the urea clearance and the blood urea concentration in relation to extrarenal azotemia and to renal disease is discussed in chapters XXI and XXII.

COMPARATIVE PHYSIOLOGY OF UREA EXCRETION

The low permeability of the renal tubules to urea is not only physiologically important but notable in view of the circumstance that urea penetrates all tissues and hence is distributed throughout the body water, while it penetrates most other living cells with ease. A noteworthy case of differential permeability is the respiratory epithelium in the gills of the teleost (bony) fishes, which has such a low order of permeability to water that the organism can withstand the relatively great osmotic gradient between sea water ($\Delta = -1.85°$ C.) and blood ($\Delta = -0.6$ to $0.8°$ C.); yet urea diffuses freely across this epithelium and the bulk of urea formed in metabolism is excreted by this route, with only traces in the urine[1917]

The contrary situation exists in the elasmobranch (cartilagenous) fishes, the sharks, rays, skates and chimera; here the respiratory epithelium, and presumably all the epithelium lining the branchial cavity, is so impermeable to urea that this compound is present in the blood in concentrations of 2000 to 2500 mg/100 cc., as opposed to zero concentration in sea water. In the elasmobranch fishes, urea is actively reabsorbed by the renal tubules, the U/P ratio ranging normally from 0.10 to 0.5;[891, 1918, 1921, 1922] the resulting physiological uremia serves to elevate the osmotic pressure of the blood and to promote the branchial absorp-

tion of water from sea water, thus obviating the necessity of drinking sea water, as is required in the teleosts.[1926,1931] Phlorizin increases the urea U/P ratio slightly, but this may be attributable to the accompanying diuresis, which invariably has the same effect. In the fresh-water elasmobranchs the urine flow is large, the urinary excretion of urea is greater, and the blood concentration is reduced to about 650 mg/100 cc. The slow loss of urea through the gills in both fresh- and salt-water forms serves to take care of the requirements of excretion in the face of continuous renal reabsorption

It has already been noted (p. 26) that urea is excreted by the tubules in the frog but not in *Necturus*,[1395,1399,2134,2135] and it is worthy of mention that *in the frog the excretory process is characterized by some sort of* limitation in the rate of transfer, as in tubular excretion in general There appears to be slight tubular excretion of urea in the aglomerular fish (in the sense of a U/P ratio greater than 1.0), but in the glomerular teleosts filtration appears to be the only process involved.[841] There is a tentative suggestion of tubular excretion in *in vitro* cultures of the chick mesonephron.[1672]

In the chicken, urea is excreted much as in the mammal,[1639] with a urea/inulin clearance ratio averaging 0.74 Under glucose diuresis, the inulin U/P ratio was decreased to 1.0 and the urea/inulin clearance ratio increased to 1.0.[1161] However, because nearly all metabolic nitrogen in the birds is degraded to uric acid, the normal urea content of chicken plasma is only 0.0 to 1 7 mg. per cent (ch. v).

CHAPTER V

Clearances Involving Active Tubular Reabsorption

Many substances of small molecular weight (glucose, amino acids, etc.) must be assumed to be present in the glomerular filtrate in the same concentration (per kg. of water) as they are present in the plasma; since these substances are normally absent from the urine, or present in the urine in a lower concentration than in the plasma, it follows that the tubules reabsorb them against a concentration gradient, a process that cannot occur by diffusion but requires the expenditure of energy, just as in the case of tubular excretion.

Little is known about the enzyme systems involved in tubular transport, either reabsorptive or excretory, but it is not surprising that on quantitative study both tubular reabsorption and tubular excretion are revealed to be limited by maximal rates characteristic of each substance. The presence of such maximal rates, coupled with the absence of any such limitation in the process of glomerular filtration, imposes on the overall process of excretion certain quantitative relations which, except for absolute magnitude, are similar for all substances that are actively reabsorbed, on the one hand, and for all substances that are actively excreted, on the other. It is therefore convenient to treat together in the present chapter those clearances which involve reabsorptive maxima, and in the succeeding chapter those which involve maxima in tubular excretion.

GLUCOSE

The essential principles of tubular reabsorption are well illustrated by the mechanism of the excretion of glucose. As stated above, glucose is not excreted by the aglomerular fish kidney when the blood glucose is greatly elevated, or after the administration of large doses of phlorizin, which induces copious glucose excretion in all glomerular forms. The inference from this fact is that, glucose being a valuable metabolite, the vertebrate kidney has never had occasion to evolve a mechanism for the tubular excretion of this substance. Since glucose is present in the glomerular filtrate in the same concentration as in the plasma water, the fact that it is normally absent from the urine indicates that it is reabsorbed by the renal tubules. Micropuncture studies show that this reabsorption occurs in, and is limited to, the proximal tubule. Glucuresis in glomerular forms is therefore attributable to incomplete tubular reabsorption under circumstances in which the load of filtered glucose exceeds the maximal reabsorptive capacity of the tubules.

Glucose is normally present in the urine in only the faintest traces, but when the plasma level is elevated above a critical value it is excreted in considerable quantities. This fact constitutes the basis for the concept of a renal 'threshold,' a term first used by Claude Bernard (1877) and more commonly associated with glucose than with any other substance. Moderate glucuresis attributable to hyperglucemia attends a large number of circumstances which may be considered entirely physiological, i.e. after a large carbohydrate meal, during severe exercise or accompanying marked sympathetic activity, as in emotional excitement, exposure to cold, etc. The most noteworthy instance of glucuresis, however, is in diabetes mellitus; it was from the sweet taste of the urine that this disease derived its name (honey diabetes) and the presence of glucose in the urine still constitutes an important diagnostic sign. Here a cyclical or maintained hyperglucemia is responsible for glucuresis; as in physiological glucuresis, the excretion of glucose occurs because the filtered load of glucose exceeds the reabsorptive capacity of the tubules and not because of any impairment of tubular function.

MAXIMAL RATE OF TUBULAR REABSORPTION OF GLUCOSE

The mechanism of glucose reabsorption can be examined by determining the rate of glucose filtration simultaneously with the rate of excretion. It has been demonstrated that glucose is completely filtrable from the plasma.[1076,1656,2156] The load of glucose delivered to the tubules is therefore given by the product of the concentration of glucose in mg/cc. in the glomerular filtrate $\left(P_G \frac{100}{W}\right)$ times the filtration rate of water in cc/min. In the routine inulin (or creatinine) clearance determination (C_F), however, the plasma concentration of inulin (or creatinine) is ordinarily determined and expressed per cc of *plasma*, and hence the true filtration rate of water is $C_F \frac{W}{100}$. On multiplying these two terms together $\left(P_G \frac{100}{W} C_F \frac{W}{100}\right)$, the load of filtered glucose becomes simply $P_G C_F$ *

The rate of tubular reabsorption of glucose, T_G (mg/min.), is the difference between the filtered load and the quantity of glucose excreted per minute, $U_G V$:

$$(1) \qquad T_G = P_G C_F - U_G V$$

where U_G is the urine glucose concentration in mg/cc. and V is the urine flow in cc/min

Shannon and Fisher[1664] and Shannon, Farber, and Troast[1663] have shown in the dog that as the (arterial) plasma concentration of glucose is progressively elevated, a point is ultimately reached where the tubular reabsorption of glucose reaches a constant, maximal rate. All maximal rates of tubular transport are conventionally indicated by Tm, using an appropriate suffix to indicate the solute involved. Thus the maximal rate of reabsorption of glucose is designated glucose Tm and indicated by Tm_G.

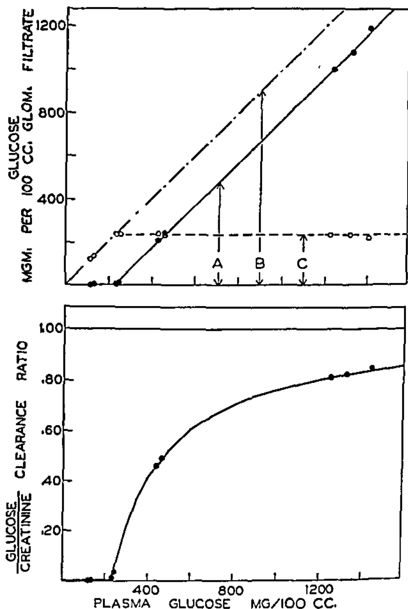


FIGURE 16. The excretion of glucose in relation to plasma concentration in the dog.

The tubules are apparently capable of reabsorbing approximately all the glucose up to a fixed, constant quantity (C) per unit time (Tm_G) At normal plasma levels reabsorption is complete and no glucose is excreted, hence the glucose/

Ni and Rehberg,[1319] the first to make a quantitative approach to this problem, used the exogenous creatinine clearance to measure the filtration rate in man. Possibly because of this fact, and possibly because of the non-specificity of their glucose method, their results failed to reveal a maximal rate of reabsorption; rather they concluded that the limiting factor in reabsorption was probably a concentration difference across the tubule (see Shannon and Fisher). Ni and Rehberg's study is, however, of historic importance.

. Below the critical level of plasma glucose required to effect tubular saturation, reabsorption from the urine is essentially complete; above this critical level, such glucose as is filtered in excess of the maximal rate of reabsorption is excreted in the urine. The maximal rate of reabsorption, as measured for the two kidneys, is independent of the plasma glucose level in the dog between the minimal saturating level (typically about 200) and 2000 mg/100 cc.

Data on glucose reabsorption in a dog are given in figure 16, which shows four consecutive sets of observations, the first at a value of P_G insufficient to saturate the tubules, and where all filtered glucose is reabsorbed: $T_G = P_G C_F$ and hence $U_G V = 0.0$; the second at a value of P_G just sufficient to saturate the tubules, but where reabsorption is still complete; the third where P_G is in excess of that required to saturate the tubules and frank glucose excretion has begun; and the fourth where P_G is very high and $U_G V$ is large In the second, third, and fourth sets of observations, T_G has remained constant, i.e. Tm_G has been reached.

So long as a constant amount of glucose is reabsorbed from the filtrate, the glucose clearance can never rise as high as the filtration rate but will approach this value asymptotically as P_G is ... and higher values, as shown in figure 16. ... creatinine clear-

i

eased and

creatinine clearance ratio is zero. As the plasma conc... is equal to the filtered load comes to exceed Tm_G, the quantity excreted (A) is equal t[o] the difference between the filtered load (B) and Tm_G Consequently, the glu[cose]/creatinine clearance ratio (below) increases with the plasma concentra[tion], approaching 1.0 as a limiting value. The smooth curve shown was calcu[lated] by assuming Tm_G = 234 mg/min per 100 cc of filtrate.

The data are arbitrarily corrected to 100 cc. of filtrate to eliminate fluctu[a]tions attributable to timing and emptying errors (Shannon and Fisher[1864])

ance ratio to P_G is:

$$\text{(2)} \qquad \text{glucose clearance} = U_G V / P_G$$

and

$$\text{(3)} \qquad U_G V = P_G C_F - Tm_G$$

Substituting (3) in (2)

$$\text{(4)} \qquad \text{glucose clearance} = C_F - Tm_G / P_G$$

$$\text{(5)} \qquad \frac{\text{glucose clearance}}{\text{creatinine clearance}} = 1 - \frac{Tm_G}{P_G C_F}$$

Examination of (5) shows that the clearance ratio will be small when $P_G C_F$ is small relative to Tm_G, and that it will approach 1.0 as P_G approaches infinity.

There is no evidence that the glucose reabsorptive mechanism is subject to 'fatigue' in consequence of long-continued saturation from hyperglucemia or that it needs to be 'activated' by an excitatory process of any kind. It appears to represent a continuously active system operating in accordance with the mass load, and limited by a maximal rate which is determined by the nature and quantity of its enzymatic components. Glucose Tm is *fairly constant and reproducible in any one animal.* It is independent of the filtration rate and consequently glucuresis may occur at different plasma glucose levels in the same animal, depending on the filtration rate.*

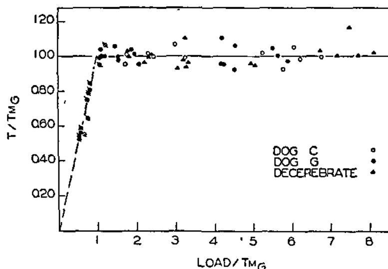
It may be presumed that glucose is reabsorbed by the proximal tubule in the dog and man, and consequently Tm_G may be considered to be one index of the functional reabsorptive capacity of the proximal tubular tissue in any one individual.†

* The administration of saline simultaneously with glucose probably increases glucose excretion during hyperglucemia in part by increasing the filtration rate.[463, 2066]

† Other maxima in tubular reabsorption will be subsequently described (phosphate, sulphate, amino acids, creatine, vitamin C, etc.) as well as maximal in [illegible]) It is obvious

Glucose Titration Curve

The relations shown for glucose in figure 16 and in equation (5) may be generalized to cover a large number of substances for which a reabsorptive maximum exists, i.e. equation (5) may be



[illegible] Relation between glucose reabsorption in the dog and filtered

1 0 The crossed symbols indicate observations where more than 99 per cent of the filtered glucose has been reabsorbed. (Shannon and Fisher [1864])

written without specific subscripts:

$$(6) \qquad \frac{\text{clearance}}{C_F} \approx 1 - \frac{Tm}{PC_F}$$

Both C_F and Tm will vary in different individuals, while C_F will vary in the same individual at different times It is therefore convenient to express the two variables concerned, PC_F and T, as *percentile* fractions of Tm itself This is equivalent to dividing both sides of equation (1) by Tm:

$$(7) \qquad \frac{T}{Tm} = \frac{PC_F}{Tm} - \frac{UV}{Tm}$$

Here T/Tm is the *fractional saturation of the tubules*, and PC_F/Tm becomes what we may call the *load/Tm* ratio; as the load/Tm ratio rises to 1.0, T/Tm reaches 1.0 and remains at 1.0 as the load/Tm ratio is increased to higher values. This method of presentation allows individuals with different values of C_F and Tm_G to be included on the same graph, as in figure 17.

We may speak of the generalized graphic representation in figure 17 as a *titration curve*, in the sense that we have titrated the tubules to saturation by the progressive elevation of the load.

GLOMERULAR ACTIVITY

The ratio C_F/Tm_G can be conceived to be one expression of 'glomerular activity,' i.e. the rate of filtration relative to the glucose reabsorptive capacity of the kidneys as a whole. The fact that all the tubules saturate at close to the same value of P_G in the dog implies that the filtration rate/maximal reabsorptive capacity ratio in each nephron (c_f/tm_g) must be nearly the same, for if this ratio differed greatly in various nephrons, a very high value of P_G would be required to effect saturation of the tubules in those with a small ratio, while those in which the ratio was large would saturate at a low value of P_G. Under these circumstances the titration curve would show considerable splay, as in A, figure 17. The glucose titration curve can therefore be used quantitatively to examine the dispersion (in the biostatistical sense) of glomerular activity among various nephrons, so long as it can be assumed that there is no splay in the titration curve of individual nephrons (ch XV).

The dog is unique in that glomerular activity, defined as above, is quite uniform throughout the kidneys, all nephrons saturating at the same value of P_G. In man the glucose titration curve has a considerable splay, the data indicating that glomerular activity ranges from 0.60 to 1.6 times the mean glomerular activity for the kidneys as a whole: i.e. in no appreciable number of nephrons is glomerular activity less than 60 per cent or greater than 160 per cent of the mean value (fig. 18).[1931,1939]

Shannon, Farber, and Troast [1863] found in the dog that tubular reabsorption, if measured when the plasma glucose concentration is falling, is significantly low (0.94) relative to Tm_G measured at a

constant plasma level. The difference apparently could not be accounted for by dead space error, and they inferred that a rapidly falling blood glucose level may influence tubular reabsorption itself. This question has been re-examined in man by Nielson,[1528] who finds that at high, steady rates of urine flow the plasma glucose level is the same 3 min. before the onset and cessation of glucosuria, implying that there is no difference in tubular activity on rising and falling plasma curves. However, the time for the disappearance of glucosuria on a falling curve can be greatly prolonged when the urine flow is low because of dead space error. Nielson also emphasizes that clearance determinations made on falling urine flows are fallacious. Such critical measurements are wholly reliable only under conditions of a fairly constant plasma concentration, and fairly constant rates of urine flow.

Cushny believed that the tubules reabsorbed a perfected Locke's fluid, a solution containing glucose, amino acids and similar food substances, sodium, potassium, chloride, urea, uric acid, phosphate, etc., in approximately the proportions in which they are of advantage in normal plasma, the fluid absorbed being 'always the same, whatever the needs of the organism at the moment.' It is now clear, however, that not only glucose but amino acids, phosphate, vitamin C, and other substances are reabsorbed essentially by independent processes, each limited by a maximal rate of transfer. There is no reason to believe that the reabsorption of glucose is specifically related to the reabsorption of other substances (excluding other sugars), and only in the case of sodium are there reasons to believe that the reabsorption of a solute is specifically related to the reabsorption of water. These reabsorptive processes must depend on highly specific cellular mechanisms. They are probably carried on more or less independently and may even occur at different positions along the tubule.

KINETICS OF GLUCOSE REABSORPTION

Shannon[1359] has conceived that during tubular reabsorption glucose enters into reversible combination with some element in the tubule cells, present in constant but limited amount, and that the subsequent decomposition of this complex limits the rate of glucose transfer from

tubular urine to blood.* The conditions to be satisfied require two consecutive reactions:



$$(8) \qquad A + B \rightleftharpoons AB \rightarrow T + B$$

where A is the glucose in the tubular urine, B the cellular element, AB the compound formed by the reversible combination of these two, and T the glucose distal to the initial reaction (i.e. in the tubule cell or the renal interstitial fluid).

In order to arrive at a maximal rate of reabsorption, the second reaction must be a first order process, its rate slow in relation to the rate of attainment of equilibrium in the first It is implicit in the first reaction, $A + B \rightleftharpoons AB$, that this step is effected at the expense of the free energy *of the reactants* However, the designation of the second reaction as a first order process does not preclude the possibility that it *may* be complex and involve an increase in free energy, which it unquestionably does.

The equation (based on the law of mass action) that relates the arterial plasma concentration, P_G (mg/cc.), the rate of glucose reabsorption, T_G (mg/min.), and the maximal rate of glucose reabsorption, Tm_G (mg/min.), in terms of this hypothesis, is

$$(9) \qquad K = \left(P_G - \frac{T_G}{C_F}\right)\left(\frac{Tm_G - T_G}{T_G}\right)$$

where K is the equilibrium constant, and C_F is the volume of glomerular filtrate in cc/min. According to equation 9, it is to be expected that small concentrations of glucose will appear in the urine at normal values of P_G, that there will be little increase in the rate of excretion ($P_GC_F - T_G$) as P_G rises until the load (P_GC_F) approaches Tm_G, and that Tm_G will thereafter be rapidly attained.

As the tubular urine moves down the nephron, progressive saturation of the cells of the proximal tubule probably occurs, and frank glucuresis begins in any nephron only when the most distal cells are presented with more glucose than they are capable of reabsorbing. This fact is neglected in taking the equilibrium concentration of glucose in the tubular urine as ($P_G - T/C_F$); consequently K in the equation above has an artificially elevated value. Moreover, reabsorption of water in the proximal

* As Shannon and Fisher note, there is no reason to suppose that the reabsorp- [illegible] homogeneous, *and* [illegible] em is complex, [illegible] initial quanti-

tubule will increase the concentration ($P_G - T/C_F$) by some multiple which automatically becomes incorporated in the constant K. This oversimplified analysis is unavoidable at the present time.

A curve calculated from equation 9, using K = 0.2 and $Tm_G = 240$, follows closely the two lines in figure 17. The splay in the angle of the titration curve is so small that the theoretical T/Tm curve is only 1 per cent removed from the linear relationship at load/Tm ratios of 0 93 and 1 07.

Shannon's theory treats the entire kidney as a single nephron and neglects the probability that the ratio of glomerular filtrate per unit of glucose reabsorptive power in individual nephrons varies considerably among different nephrons Any dispersion of glomerular activity is artificially incorporated in K of equation 9 There is, at present, no way of knowing what the titration curve of a single nephron may be like, except to suppose that it must be a very sharp angle; glucose can be almost completely reabsorbed in the first half of the proximal tubule of the frog, and as P_G increases one may suppose that the zone of saturation moves distally until saturation of the most distal cells occurs, when glucuresis in that nephron will begin abruptly In any case, the titration curve of a single nephron must present a sharper angle than that of the entire kidneys

GLUCOSE Tm IN MAN

Smith, Goldring, Chasis, Ranges, and Bradley [1931 1939] report that Tm_G in normal subjects averages 375 ± 79.7 mg. in 24 men, and 303 ± 55.3 mg. in 11 women (both figures corrected to 1.73 sq. m. body surface area) * The mean filtration rate may be taken as 127 cc. in males and 117 cc. in females; nominally complete saturation of the tubules might be expected at 2.99 and 2.59 mg. of glucose, respectively, per cc. of *arterial* plasma. Actually, the values of Tm_G and C_F vary in different individuals through such a range that average figures are of little use, and, moreover, detectable glucuresis can be expected in most individuals at 60 per cent of the nominal saturation value of P_G because of the early saturation of nephrons with high glomerular activity. Again, using the mean male figures $Tm_G = 375$ and $C_F = 127$, at the normal value of P_G *(1.0 mg.) the filtered load is equal to only slightly more* than one-third of Tm_G. Hence the filtration rate could be more

* The reader may be reminded that all clearance and Tm figures are in cc/min. or mg/min unless otherwise stated. The practice throughout this volume is to report the mean and standard deviation of the distribution, σ.

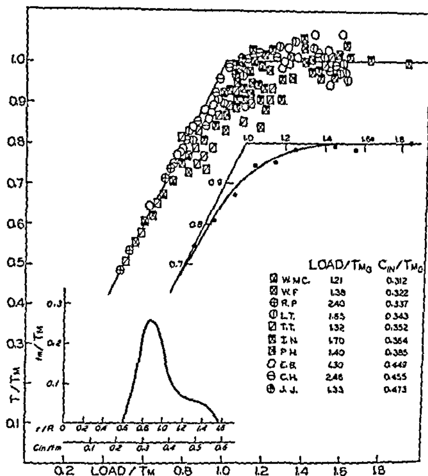


FIGURE 18. Normal dispersion of glomerular activity. Mass plot of glucose titrations on 10 normal subjects, some of whom were titrated on 2 or more occasions. The mass plot shows more scatter than is present in any 1 individual,

Tm = 0.1. These averaged observations are shown by the dots in the inset,

The ratio c_{in}/tm indicates absolute values of glomerular activity.

The frequency distribution curve as drawn would indicate that in a small proportion of nephrons relative glomerular activity (r/R) is greater than would be expected from chance distribution alone, with the consequence that the mode

than doubled without producing glucuresis, and it is rare for the filtration rate to be increased by more than 50 per cent.

Figure 18 shows the dispersion of glomerular activity among the nephrons of the normal human kidney, as judged by titration with glucose. The topic of glomerular activity is discussed further in chapter xv.

Glucose Tm is reproducible in man: of 20 repeated determinations, in the study above, 16 agreed within 5 per cent, the others differing by 6, 6, 8, and 12 per cent. It is not influenced significantly by adrenalin, caffeine, or renal hyperemia induced by pyrogen; adrenalin reduces renal blood flow without greatly changing the filtration rate, caffeine reduces renal blood flow with a slight increase in filtration rate; while during renal hyperemia the renal blood flow may be increased by 20 to 80 per cent without marked changes in filtration rate. Glucose Tm is not influenced by the infusion of acetate or lactate in the dog, as is tubular excretion.[1490] The most noteworthy conclusion to be drawn from these observations is that, since glucose Tm is neither increased nor decreased by circumstances that increase glomerular pressure (adrenalin and caffeine) or total renal blood flow (hyperemia), glomerular activity in the normal human is not only relatively uniform but extremely stable. (Govaerts and Lambert [827] report an average for the Tm_G/C_F ratio of 2.41 ± 0.345 in 45 normal subjects, which corresponds to a C_F/Tm_G ratio of 0.415.)

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is shifted to slightly below the mean However, the use of data from different individuals, combined with the narrow limits of dispersion, cautions against attaching significance to minor changes in the frequency distribution curve, which is extremely sensitive to changes in the angle of the titration curve. The frequency distribution curve must therefore be considered as practically identical with the symmetrical normal frequency distribution So interpreted, it may be said that glomerular activity in the normal kidney is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the observations fall within ±40 per cent of the mean (In some individuals, such as J J, E B,

In conditions in which the filtration rate is decreased, as in diabetic coma, dehydration, shock, congestive heart failure, amyloidosis, intercapillary glomerulosclerosis, etc., the plasma glucose level at which glucuresis begins may be expected to be correspondingly elevated.[1304, 1995] However, the data of McCance and Widdowson [1104] on subjects in diabetic coma show an exogenous creatinine/inulin clearance ratio substantially below 1.0 (0.42 to 0.85), indicating that the renal tubules may be so injured by ischemic anoxia or toxic factors as to suffer an increase in permeability. This circumstance, if factual, would further diminish glucose excretion.

The ratio C_F/Tm_G in adult normal men in the study above averaged 0.371 ± 0.0563. The coefficient of variation (σ/mean) is about 15 per cent, indicating a degree of constancy almost equal to that of the filtration rate, which has a coefficient of variation of 14.2 per cent, as good as most physiological variables. That is, the relative development of filtration rate and glucose reabsorbing capacity are parallel in different individuals, as in different nephrons in any one individual. The correlation coefficient between the two terms is low (0.656), however, possibly because of the small range of values in the subjects studied

In 1921 Hagedorn,[884] by graphic computation of simultaneous blood and urine glucose analyses from a diabetic patient, showed that, at a value of P_G slightly above the 'threshold,' the rate of glucose excretion became proportional to the blood glucose concentration, as shown by the line marked 'excreted' in figure 19. Extrapolation of this line to its point of intersection with the abscissa (L) yields a nominal value of blood glucose at which excretion would begin were there no splay in the titration curve. This nominal threshold, as Nielson [1327] notes, may be called the 'line threshold.' The value of the 'line threshold' may be calculated by dividing Tm_G by the *average* value of C_F. The 'line threshold' will exceed the actual value of P_G at which the first trace of glucose is excreted by an amount determined by the splay in the titration curve, and hence the difference between the two affords an index of the degree of splay.

Govaerts, Lambert, Lebrun, and de Braucourt [825] have used the relationship $\Delta UV/\Delta P = C_F$ on a falling plasma glucose curve to measure the filtration rate in 17 subjects during hyperglucemia. The figures so obtained agree well with the simultaneous thiosulphate clearance, and the average value of Tm_G calculated from extrapolation of the data to L (245.2 mg) agrees well with that calculated from the thiosulphate

clearance (252.8 mg) In the method of calculation, however, it must be *assumed* that both C_F and Tm_G remain constant throughout the course of observation.

On the same assumptions, the value P_G per 100 cc of filtrate (or $\bar{P}_G$) (the 'line threshold' divided by C_F and multiplied by 100) nom[illegible] required to effect tubular saturation may be calculated during glu[illegible]

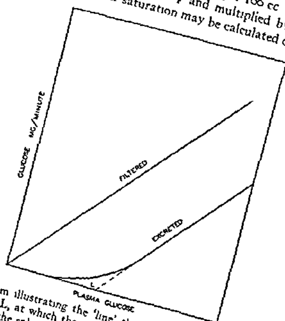


FIGURE 19 Diagram illustrating the 'line' threshold value of the plasma glucose concentration, L, at which the renal tubules are nominally just saturated This value neglects the splay in the excretion curve which may be large if there is a wide dispersion in glomerular activity (Govaerts, Lambert, Lebrun, and de Heinzelin de Braucourt [illegible])

without measurement of the urine volume, and hence without the accurate collection of urine Rearrangement and appropriate substitution in equation 2 yields

(10)
$$\bar{P}_G = P_G - \frac{P_{IN}}{U_{IN}} U_G$$

all of which terms are concentration terms. Foldi, Szabo, and Zsoldos [illegible] have called this value ($\bar{P}_G$) the 'aglucosuric blood sugar concentration' and designated it by A_g However, Tm_G remaining constant, A_g will be increased where there is a reduction in filtration rate and *vice versa*; and, since the calculation affords no information on either the filtration rate

or on the actual value of Tm_G, *it is not clear wherein it is of any more* value than the determination of U_G at various values of P_G, without the trouble of doing inulin analyses.

The reabsorption of glucose is so effective that glucose excretion is not increased by osmotic diuresis (urea) so powerful that over 50 per cent of the water in the glomerular filtrate is excreted in the urine.[1488] Schou[1799] found that, during extreme sodium sulphate diuresis in the anesthetized (urethane) rabbit, 70 to 80 per cent of the filtered glucose was carried into the urine, but the conditions of Schou's experiments were extreme and the plasma glucose in the control periods ranged from 361 to 586 mg/100 cc., so that glucose reabsorption would be incomplete without diuresis.

CLINICAL TESTS FOR GLUCOSURIA

There are traces of glucose in the urine at all times[909] and the plasma threshold *as clinically determined* in man is highly variable, ranging *from 100 to over 200 mg/100 cc. of plasma or whole blood, although 80* per cent of normal individuals fall within the range of 140 to 190 mg. per cent.[824, 523, 1007, 1876, 2279] Nearly all available data are complicated by the use of whole blood or plasma from *venous* blood, and by the use of insensitive urine glucose methods, and have been performed without regard to urine flow. The use of whole blood in this problem is practically meaningless, and venous plasma or serum is but little better, since a large arterial-venous difference (−26 to +102 mg/100 cc.) may exist between arterial (renal) blood and blood from the antecubital vein, a difference which is not wholly abolished at high plasma concentrations. Capillary blood appears to approach arterial blood closely in its composition and to be generally satisfactory for clinical use. Assuming that the test is positive when a fixed quantity of glucose is added to the reaction mixture, much larger quantities of urine will be required to give a positive test when the urine flow is large and the urine is correspondingly dilute than when the urine flow is small.[1478, 1479] Neglect of urine flow, which may range from 0.5 cc/min. or less up to large figures during water diuresis, diminishes the quantitative sensitivity of the test. Moreover, at low urine flows a correction for renal delay time of at least 6 min., and probably more than this, is indicated. Lastly, variations in the splay of the titration curve associated with functional or pathological changes in the renal circulation will be important if the urine test is really quantitative and sensitive. Consequently, only a qualitative statement with respect to 'glucose threshold' can be made by ordinary clinical methods.

GLUCOSE REABSORPTION IN THE FROG

The reabsorption of glucose in the bullfrog, *Rana catesbiana*, is characterized by a maximal rate which has an average value of 35.6 mg/kg per hr. In one animal this figure represented about 160 mg/100 cc. of glomerular filtrate The frog differs from the dog and man in that, at values of P_G below that where $P_G C_F = Tm_G$, reabsorption remains incomplete (some nephrons are saturated), while a load twice as large as Tm_G is required to effect saturation of all nephrons; i.e. there is a large splay in the titration curve. Complete saturation is not reached until P_G = 300 mg/100 cc. Forster [676] attributes this to variations in glomerular activity, some glomeruli being very active and some relatively inactive.* Wood [2270a] reports that maximal glucose reabsorption was obtained in individual *Necturus* proximal tubules at values of P_G as low as 44 mg/100 cc.

If P_G is maintained between 300 and 900 mg/100 cc., Tm_G increases in proportion to the filtration rate, the ratio being 156 mg/100 cc. of glomerular filtrate This indicates that variations in glomerular activity involved an 'all or nothing phenomenon,' since if activity were partially reduced in some glomeruli at such high values of P_G, Tm_G should be only slightly affected by changes in the filtration rate.

PHLORIZIN GLUCURESIS †

Of particular interest in connection with the excretion of carbohydrates is the action of the glucoside, phlorizin, which is contained in the bark and roots of apple, pear, and other fruit trees, in blocking sugar reabsorption by the tubules. Shortly after its isolation by de Koninck in 1846, this investigator tried phlorizin in the treatment of malaria because it was bitter, like other remedies which were effective in this disease. This prescription was short-lived, however, and it was not until 1885 that von Mering discovered that phlorizin caused transient glucuresis. In 1899, Minkowsky and von Mering demonstrated that diabetes mellitus could be produced experimentally in dogs by the extirpation of the pancreas, and they correctly attributed the disease to a deficiency of the internal secretion of this organ. Because the action

* See chapter xv for discussion of glomerular activity in relation to the control of urine flow in the frog and other cold-blooded animals

† Phlorhizin, phloridzin, phlorrhizin Phlorizin is, however, the preferred spelling in both the Oxford and Webster's Dictionary.

of phlorizin was accompanied by the excretion of glucose in the urine, glucuresis came to be called phlorizin 'diabetes,' and it was many years before the fundamental differences between the two conditions were fully recognized.

By reference to the creatinine clearance in the dog, or the inulin clearance in other species, it has been shown that in sufficient doses (200 mg/kg. *intravenously of a freshly prepared solution* in sodium bicarbonate in the dog) phlorizin completely blocks the reabsorption of glucose in the dogfish,[1845] the teleost fishes,[1625] chicken,[1628, 1655] sheep,[1851] dog,[1620, 1622, 1646, 1847, 1866] and apes;[1936] in the largest doses given to man[247 1868] (100 mg/kg.) it raised the glucose/inulin clearance ratio to 0 91, but it is certain that larger doses would produce complete glucuresis. Phlorizin is poorly absorbed from the gastrointestinal tract and complete glucuresis cannot be obtained by this route;[803] complete glucuresis is probably rarely obtained after subcutaneous administration; after intravenous administration it remains complete for only 2 to 3 hr.

Phlorizin in adequate doses blocks the tubular reabsorption of the pentose xylose, raising the average xylose/inulin clearance ratio from 0.78 to 1.02 in the dogfish,[1848] the xylose/creatinine ratio from 0.72 to 1.00 ± 0.05 in the dog[1620, 1622 1626, 1866] and the xylose/sucrose ratio from 0.78 to 1.02 in the rabbit.[604] The largest doses administered to man (100 mg/kg. intravenously)[1868 1868] raised this ratio from about 0.79 to 0.89. In the phlorizinized bullfrog and turtle[674, 698] the glucose, xylose, and creatinine clearances are identical but about 12 per cent below the inulin clearance, probably as a result of injury and increased permeability of the tubules.

Phlorizin partially blocks the reabsorption of vitamin C,[1608] but no other normal constituent of the glomerular filtrate is known to be affected: chloride and bicarbonate,[1866] creatine,[1622] amino acids,[1630] urea[1846, 1868] or hexamethylenetetramine[1626] excretion continue unaffected. Phosphate reabsorption is slightly accelerated in the phlorizinized dog, probably because of the exclusion of glucose from a transfer mechanism for which phosphate and glucose compete.[1635]

Phlorizin depresses the tubular excretion of phenol red in the chicken[1628] and in man;[358] of diodrast in man[205] and in the

dog; [2194] of creatinine in the dogfish,[291, 1844, 1845] chicken,[1855] chimpan-
zee [1936] and man; [1845] and of creatine in the teleost, *E. morio*.[1625]
This inhibitory effect on tubular excretion may be a consequence
of diversion of energy rather than a specific interference with the
transport mechanism. It does not block the tubular excretion of
creatine in the dogfish in doses adequate to produce complete
glucuresis,[1629] the only negative result with respect to tubular ex-
cretion so far recorded.

The administration of phlorizin causes a marked reduction in
all clearances by profound circulatory effects, which circumstance
makes it necessary to assess its action on renal clearances in terms
of simultaneous clearance ratios rather than absolute values.[802 1803,]
[1622 1626, 1628 1928 2208] In the sculpin it causes the glomerular circula-
tion to shut down entirely, thus temporarily rendering the animal
aglomerular [1403]

Phlorizin glucuresis in all animals is accompanied by hypo-
glycemia, owing to rapid loss of glucose from the body, and by
moderate diuresis, owing to the osmotic resistance offered by the
urinary glucose to the reabsorption of water. Prolonged ad-
ministration leads secondarily to a rise in protein combustion,
ketosis, and many other sequellae associated with deficient car-
bohydrate metabolism.[1845]

Little is known concerning the mechanism of its action, which
is primarily confined to the kidney and does not include any di-
rect effect upon the body as a whole or upon the oxidation of glu-
cose. It does not inhibit the metabolism of excised renal tissue [1882]
or the fermentation of yeast,[468] although it does inhibit the selec-
tive absorption of sugars from the intestine. In sufficient concen-
tration it inhibits phosphorylation of glucose, and its action on
the tubules is possibly related to phosphatases [1345, 1388] (The aglo-
merular fish kidney, which is not involved in glucose reabsorption,
contains no alkaline phosphatase [2230]) Arbutin, a glucoside ob-
tained from the bearberry, also induces marked glucuresis, but
amygdalin (bitter almonds) and salicin (willow) are without
marked glucuretic action.[1442]

Ever since von Mering's discovery of the glucuretic action of phlorizin,
this drug has been used experimentally to force the excretion of glucose
in connection with metabolic investigations, and it was early introduced

for this purpose in quantitative studies in renal physiology.[1076,1652,2168] It has long been accepted that phlorizin glucuresis is due to inhibition of glucose reabsorption *rather than to stimulation of* glucose excretion by the tubules.* [1345] The first investigator to use phlorizin in quantitative studies of renal function was Mayrs,[1423] who conceived that if it completely blocked the reabsorption of glucose, this sugar should show the same U/P ratio as a 'no-threshold' substance. For his 'no-threshold' substance in the rabbit he chose sulphate, which would not have been unfortunate, since at elevated plasma levels tubular reabsorption is probably small relative to the total filtered load. But unfortunately he administered phlorizin subcutaneously in inadequate doses (200 mg/kg.) (it is poorly absorbed), with the result that the U/P ratio of glucose rose to a value equal to that of sulphate in only one experiment, and he erroneously concluded that glucose reabsorption could not be completely blocked by phlorizin.

Later Poulsson[1652] utilized *phlorizin in an attempt to measure the* filtration rate. He compared simultaneous glucose and creatinine clearances in phlorizinized dogs, obtaining one clearance ratio as high as 0.96 and several between 0.80 and 0.90; he administered phlorizin subcutaneously, however, and his glucose method was sensitive to phlorizin itself as well as creatinine,[1868] which facts no doubt account for his failure to obtain better correspondence between clearances. His belief that the approximate convergence of the glucose and creatinine clearances in the phlorizinized dog afforded a final proof of the filtration-reabsorption hypothesis is subject only to the criticism that it was not yet proved that creatinine might be excreted by the renal tubules (as it is in fishes, the chicken, the chimpanzee, and man) and that phlorizin might block this excretory process (as it has been shown to do in the dogfish, chicken, *and man). It has, however, subsequently been demonstrated that there* is no tubular excretion of creatinine in the dog, and Mayrs' and Poulsson's utilization of phlorizin, as Mayrs' utilization of the simultaneous U/P ratios of creatinine, sulphate, and phosphate, are of historic moment in the history of renal physiology.

Jolliffe, Shannon, and Smith,[1075] giving 100 to 200 mg. of phlorizin intravenously to dogs and using more specific sugar methods, were the

* Conway *et al.*[399] adhere to the view that phlorizin induces tubular excretion . . . ed the conclusions reached by Walker . . . in micro- . . . grounds that the data are misinterpreted. In view of the total evidence cited in this chapter, however, belief in the tubular excretion of glucose is untenable.

first to report consistent identity of clearances (glucose, xylose, sucrose, and raffinose) in the phlorizinized animal. It was not until the introduction of inulin that the creatinine clearance was validated as a measure of the filtration rate in the dog, and that the identity of the glucose-creatinine clearance ratio in phlorizinized animals acquired significance.

Lambrechts [1198] reports extensive pharmacological studies on this and related glucosides.

XYLOSE

The xylose/inulin clearance ratio averages 0.78 in the dogfish,[1845] 0.81 in the sculpin,[389] 0.82 in the frog [674] and turtle,[695] 0.60 in the rabbit,[1090] 0.73 in the dog,[1670, 1848] and 0.78 in man.[1389] The xylose/creatinine clearance ratio averages 0.65 in the rabbit [404] In the dog the xylose/inulin ratio is only very slightly increased (0.80 to 0.90) by raising the plasma xylose concentration from 50 to 500 mg/100 cc., but when the plasma glucose concentration is raised to 300 mg/100 cc., a level high enough to saturate the glucose reabsorbing mechanism, the xylose/creatinine clearance ratio in the dog increases to 1.0 [1852] Similarly, saturation of the tubules with glucose partially or completely blocks xylose reabsorption in the frog [674] and turtle.[695]

Xylose reabsorption therefore differs from glucose reabsorption in that a maximal rate of reabsorption is not reached at easily attainable plasma concentrations, but the reabsorptive process is an active one involving the glucose transport system, as shown by the fact that it is completely blocked by phlorizin or by glucose

Shannon [1852] assumed that xylose reacts with element B in the reabsorptive system in the manner of glucose (see p. 90) with these differences: that, if the reaction $A + B \leftrightharpoons AB$ is slower than the reaction $AB \rightarrow T + B$, the first reaction never attains equilibrium and a linear relation will exist between P and T, and T/V will be small relative to P, giving a substantial value to the clearance, i e reabsorption will be of a low order and linearly related to plasma concentration Alternatively the same result will be obtained if K is increased in value Examination of the behavior of glucose and xylose indicates a value of K for glucose of 0.2, and for xylose of 300. Hence, when both sugars are in competition, even at relatively low glucose levels in the tubular urine, nearly all of the cellular element B will be in combination with glucose, and negligible reabsorption of xylose will occur Xylose reabsorption will decrease with increasing glucose concentration and be reduced to zero just above the level at which B is saturated with glucose. At this time, the xylose clearance should be equal to the rate of glomerular filtration. The [illegible]

that xylose is actively reabsorbed by the glucose mechanism but that the velocity constants are such as to permit substantial xylose excretion at low plasma levels and to prevent saturation of the reabsorptive mechanism at all practically attainable high plasma levels.

SUCROSE

When sucrose is injected intravenously into normal individuals, 90 to 98 per cent can be recovered in the urine in 12 to 24 hr. There are no enzymes in the blood or body fluids capable of hydrolyzing it.[1101] It is physiologically inert and in moderate doses has no effect upon the urea clearance.[1077]

The sucrose/xylose clearance ratio = 0.99 in the normal dogfish[1344] and 1.01 in the dog.*[1076,1077,1620] The sucrose/creatinine clearance ratio is about 0.8 and the xylose/sucrose ratio about 0.9 in the rabbit and is not greatly affected by phlorizin[404] The xylose/sucrose clearance ratio was reported in man as 0.93 by Smith,[1925] as 0.90 by Keith, Power, and Peterson,[1102] indicating that in man there is some reabsorption of xylose and sucrose, and the ratio rose to 1.01 in partially phlorizinized man.[157] However, Steinitz[1997] reports a sucrose/inulin ratio of 0.99 in normal man, a value not influenced by saturation of the glucose reabsorptive mechanism by glucose. The question remains, therefore, whether or not in man there is some reabsorption.

Since sucrose is relatively non-toxic it has been widely administered intravenously to dehydrate the tissues, especially the brain, and to induce osmotic diuresis.[831,970,971] Several reports have appeared of hydropic degeneration of the proximal tubules produced by sucrose given in this manner.[62,462,632,971,1132,1242,1728] However, the repeated administration of sucrose in physiologically reasonable amounts does not appear to produce permanent injury to the kidney.[632,969,971,972,2229] It is to be noted that, in some pathological reports on man,[62] patients had been given as much as 800 gm. (almost 2 lb.) of sucrose in 4 days when they were anuric and had no means whatever of excreting it.

FRUCTOSE

Gammeltoft and Kjerulf-Jensen[744] have demonstrated that in man, at *plasma concentrations below 15 mg/100 cc., the fructose* U/P ratio may be less than 1.0, indicating active reabsorption. U/P ratios less than 1.0 were not demonstrable in rabbits, cats, and dogs, but there is no doubt that active reabsorption also occurs in these species The fruc-

* Lower ratios, considerably out of line with those of other investigators, were reported by White and Monaghan[2206]

tose/creatinine clearance ratio in normal dogs and rabbits ranges from less than 0.1 to 0.2 at plasma levels below 20 mg/100 cc.; in cats this figure appears to be somewhat higher. In all species, as the plasma level is raised the quantity reabsorbed by the tubules increases, but at a diminishing rate; the authors state that a maximal rate of reabsorption is not reached at filtered loads of 40 mg/min. in the rabbit and cat, or 70 mg/min in man.

Phlorizin (200 to 300 mg/kg intravenously or administered daily in oil), in doses sufficient to raise the glucose/creatinine clearance ratio to the range of 0 50 to 0 91, increased the fructose/creatinine clearance ratio somewhat less (0.46 to 0 81). Complete phlorizinization was apparently not obtained.

Saturation of the reabsorptive mechanism by glucose raised the fructose/creatinine clearance ratio in the cat and man, but not above 0 79 The results indicate that some element in the reabsorptive mechanism is shared in common by these two sugars (It is noteworthy that a maximal rate of reabsorption of glucose was not reached in the cat at a load of nearly 140 mg/min See galactose for further comments)

Hansen, Jacobsen, and Petersen [907] similarly report that elevation of plasma glucose to 343 mg/100 cc in the dog, a value sufficiently high to effect saturation of the glucose reabsorption mechanism, had no effect on the fructose/creatinine clearance ratio (serum fructose = 52 to 58 mg/100 cc) This ratio was not affected by changes in urine flow from .5 to 12 8 cc/min (creatinine U/P ratio = 3 1) The clearance ratio ose, however, from 0 285 to 0 79 as the plasma fructose concentration as increased from 3 5 to 336 mg/100 cc ; the reabsorbed fructose creased at a diminishing rate but failed to reach a maximum under the nditions of the experiment The authors conclude that a considerable ctosuria is not accompanied by an increased excretion of glucose, and t, in so far as the two hexoses share a common reabsorptive system, s not that component which determines the maximal rate of reab- tion of either one

more recent studies Levine and Huddlestun [1227] report the demon- ion of a maximal rate of fructose reabsorption (in 10 kg dogs) of 60 mg/min , a value not affected by simultaneous saturation with se Phlorizin reduced this value

ou [1789] reports that fructose reabsorption is little influenced by te diuresis in rabbits at creatinine U/P ratios from 200 to 5 The ce ratio increases, but the data do not permit one to decide how f this increase is attributable to changing plasma fructose con- on

GALACTOSE

Gammeltoft and Kjerulf-Jensen[744] report that galactose behaves very much like fructose; the U/P ratio may be less than 1.0 in man; the galactose/creatinine clearance ratio ranges from 0.22 to 0.42 at plasma levels of 86 to 202 mg/100 cc.; the ratio rises with elevation of plasma level, though a maximal rate of reabsorption is not demonstrable at filtered loads of 30 mg/min. in the cat or 70 mg/min. in man. Phlorizin in the doses used partially blocked reabsorption, as did hyperglycemia

The authors conclude that fructose and galactose are, like glucose, actively reabsorbed by the tubules. They tentatively ascribe the differences in reabsorptive activity to the existence of phosphorylating and dephosphorylating enzyme systems specific for each hexose; the common feature in reabsorption they ascribe to either the energy-supplying system or the phosphate donor (adenylic acid system), leaning towards the latter since phlorizin, which impairs the reabsorption of all three hexoses, does not primarily affect oxidative processes. The competition offered by glucose would then result from rivalry to act as a phosphate acceptor to the common phosphate donor, adenosine triphosphate. In this view, the demonstration by Shannon[1852] that excess glucose completely blocks the reabsorption of xylose indicates that glucose and xylose share a common enzyme system, while glucose and fructose, and probably glucose and galactose, do not.

Eiler *et al.*[592] report that about 40 per cent of filtered galactose is reabsorbed in the dog, irrespective of plasma galactose concentration.

RAFFINOSE

The trisaccharide, raffinose, has a clearance identical with that of glucose in the phlorizinized dog. No clearance ratios are available in the normal dog.[1076]

AMINO ACIDS

The first observations on man by Kirk[1119] showed that the total amino acid clearance has a very low value, ranging from 1 to 8 cc.; after the administration of glycine the clearance rose as high as 25 cc. It is obvious that amino acids are extensively reabsorbed and it is to be expected that various amino acids would be handled differently. Doty[639] early demonstrated in the dog that tyrosine and histidine are almost completely reabsorbed when the filtration load is increased moderately, while N-methyl-L-tyrosine is less

effectively reabsorbed and N-acetyl-L-tyrosine is poorly reabsorbed at low plasma levels.

Pitts [1830] subsequently showed that the tubular reabsorption of glycine in the dog becomes nearly constant, or approaches a maximal value asymptotically, at load/T ratios above 1.5. Possibly one is warranted here in speaking of a maximal rate of reabsorption or Tm (fig. 20). Tm in 4 dogs averaged 18, 24, 30, and 32 mg.

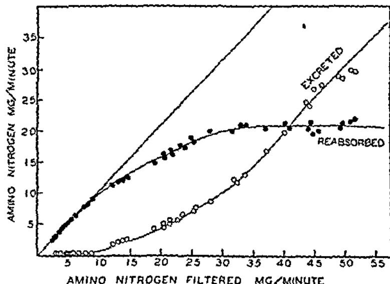


FIGURE 20 Excretion of glycine amino nitrogen in the dog in relation to the quantity filtered (Pitts [1830])

of amino acid nitrogen per min. per sq. m. of body surface area At normal plasma amino acid levels (below 10 mg. nitrogen per 100 cc), more than 98 per cent of the filtered amino acid is reabsorbed, but with rising plasma concentration T fails to increase in proportion to the amount filtered and consequently excretion becomes appreciable at a load ratio of 0.2. Variations in urine pH did not affect reabsorption.

That glycine and creatine are reabsorbed by a common mechanism is shown by the fact that, as the filtered load of glycine is increased, creatine reabsorption decreases and is reduced to zero when the reabsorptive mechanism is saturated with glycine. But

the elevation of plasma creatine concentration has no appreciable effect on the reabsorption of glycine, indicating that glycine has a much higher affinity for the reabsorptive mechanism than has creatine. This is consonant with the relatively insignificant amounts of creatine normally reabsorbed.*

Saturation of the tubules with glucose has no effect on the reabsorption of amino acids. Saturation with glycine has no effect on the reabsorption of glucose. Phlorizin in amounts sufficient to produce complete glucuresis does not increase normal amino acid excretion These results are consonant with the view that the reabsorptive mechanisms are different. However, when the plasma concentrations of glucose and glycine were raised simultaneously to saturation levels, a serious collapse of filtration rate occurred. Associated with this collapse was an approximately equivalent reduction in both glucose and amino acid reabsorptive capacities. Toxic manifestations in the presence of high plasma glucose and amino acid concentrations were extreme, including coma and a rigidity of a decerebrate type. In one instance, the animal was put aside for later autopsy, but recovered after a few hours with no residual signs of renal impairment. The depression of reabsorptive capacity in these experiments Pitts attributes to circulatory collapse and complete closure of some glomeruli, with consequent reduction in the number of tubules contributing to the reabsorptive capacity of the kidney, and not to competition for a common reabsorptive mechanism.

As in the case of glycine, reabsorption of DL-alanine, L-glutamic acid and L-arginine[1681] decreases rapidly as the load is increased. In no instance was it possible to demonstrate that a maximal rate of reabsorption was reached at loads which are practically obtainable, but the titration curves were sufficiently distinct to justify the statement that reabsorption stands in the decreasing order of glycine, alanine, glutamic acid, and arginine at all amounts filtered. Casein hydrolysate behaves in a manner intermediate between glutamic acid and alanine. Even at the lowest load, significant amounts of alanine, glutamic acid and arginine were excreted.

* Contrary to previous reports, the administration of large quantities of glycine produced no apparent injury of the kidney, despite vomiting, dilatation and fixation of the pupils, weakness and muscular unco-ordination.

Although the quantitative characteristics of the reabsorptive processes are different for the four amino acids, Pitts believed that at least three of them are reabsorbed by a common renal mechanism, as indicated by the fact that, at sufficient loads, alanine and glycine completely, and glutamic acid partly, block creatine reabsorption. The effects of arginine on creatine reabsorption are so slight as to be within the experimental error, but the amount of arginine reabsorbed at the highest load is relatively insignificant in comparison with the maximal tubular reabsorptive capacity for glycine, and it may be expected that arginine would have little effect on creatine reabsorption within the range studied However, moderate elevation of plasma glycine significantly depressed the reabsorption of arginine. While not conclusive, this suggests that arginine may be reabsorbed by the same renal mechanism which reabsorbs glycine, alanine, glutamic acid, and creatine. If so, the failure of arginine to depress creatine reabsorption would indicate that only an insignificant fraction of the total reabsorptive capacity is occupied by arginine to the exclusion of creatine.

With certain modifications, Pitts applies to glycine Shannon and Fisher's[1864] kinetic hypothesis of tubular reabsorption. Shannon nd Fisher assumed for glucose that the second or decomposition reac-on in equation 8, *viz* AB → A + B, proceeds rather slowly in lation to the rate of attainment of equilibrium in the first reaction, + B → AB. If the postulate is reversed for amino acids (as for lose), namely, that the second reaction proceeds rapidly in relation to rate of attainment of equilibrium in the first, the gradual approach a limiting tubular reabsorptive capacity finds ready explanation der conditions such that free B exists in the cell (incomplete saturation he reabsorptive system), the amount transferred is limited by the tive rate of combination of A with B Assuming total B (B + AB) constant, the rate of transport will depend upon the concentration and the specific velocity of its combination with B. The lower this ty, the more gradually will the reabsorptive system be saturated; gher this velocity, the more nearly will the amino acid system like the glucose system Pitts inclined to the view that the nces between the reabsorption of the four amino acids should be ted chiefly to differences in the rates of formation of their B xes. The lower this rate the more gradually is the reabsorptive m attained.

ompetition between creatine and glycine depends upon reaction substance common to both reabsorptive systems. If combined ine, B is unavailable to creatine, and as a consequence creatine

reabsorption is proportionately reduced. However, the affinity of glycine for B must be greater than that of creatine, for large amounts of creatine do not depress glycine reabsorption.

The data of Goettsch, Lyttle, Grim, and Dunbar [793] on the reabsorption of DL-alanine in the dog, show even less tendency to approach a maximal rate, reabsorption remaining at a high level (64 to 81 per cent) at the highest loads (40 mg. nitrogen per 100 cc.) reached Again it is demonstrated that casein hydrolysate behaves like DL-alanine (and glycine) in that it undergoes very effective reabsorption at high loads.

Eaton, Ferguson, and Byer [666] find that a maximal rate of reabsorption can apparently be reached in dogs at feasible loads with DL-valine, L-leucine, and DL-isoleucine. For valine this value averages about 13, and for leucine and isoleucine 9 to 10 mg. of amino acid nitrogen per min. per sq. m., though these figures vary considerably in different dogs There is considerable splay in the titration curve of valine and isoleucine, significant excretion beginning at a load/Tm ratio of 0 3, while reabsorption of leucine remains essentially complete until the load/Tm ratio approaches 1 0.

Using microbiological methods, Beyer, Wright, Russo, Skeggs, and Patch [161] failed to obtain a maximal rate of reabsorption in individual dogs with L-tryptophane, DL-isoleucine, DL-valine, and L-leucine at loads of 15.8, 96, 105, and 26.5 mg/100 cc. of filtrate, respectively. In general at the highest plasma levels, less than 2 per cent of the filtered amino acid was excreted. Tm for L-arginine and L-lysine in single dogs had values of 15 8 and 60 4 mg/100 cc. of filtrate, whereas saturation was not reached with L-histidine and DL-methionine at loads of 41 6 and 115 mg/100 cc. of filtrate,[2276] or with DL-threonine and DL-phenylalanine at loads of 150 and 44 mg/100 cc. of filtrate.[1752, 2274] Ferguson, Eaton, and Ashman [635] also report failure of DL-methionine to effect saturation at a load of 52 mg/100 cc. of filtrate, or 28 mg/min. per sq. m

Histidine, methionine, leucine, isoleucine, tryptophane, valine, threonine, and phenylalanine are thus characterized by such effective reabsorption that their Tm values cannot be reached by the administration of amounts that do not cause severe nausea, while glycine, arginine, and lysine are characterized by less capacity for reabsorption and show a measurable Tm.

Leucine blocks the reabsorption of isoleucine, arginine blocks the reabsorption of lysine, and *vice versa,* and the sum of the Tm values of the two compounds at elevated plasma levels approximates Tm for one of the amino acids, instead of the sum of these Tm values; histidine blocks the reabsorption of arginine and *vice versa.* However, glycine has

no effect on the reabsorption of isoleucine or leucine, and arginine and leucine do not interfere with the reabsorption of each other. Beyer and his coworkers[112] were unable to confirm Pitts'[1681] statement that glycine depresses the reabsorption of arginine. They summarize the available data on competition between amino acids by dividing them into three groups: I, the basic amino acids, arginine, histidine, and lysine; II, the mono-amino-mono-carboxylic acids, leucine and isoleucine; and, III, glycine. Amino acids within groups I and II are apparently reabsorbed by two more or less independent mechanisms, the members of each group competing with each other but not with members of the other group. A third mechanism may be concerned with glycine transport, since it was not possible to demonstrate that this amino acid interferes with the reabsorption of amino acids in either of the other two groups.

After the administration of casein hydrolysate or an amino acid mixture in clinically useful quantities and rates, the plasma concentrations of individual amino acids do not rise to critical levels such that their maximal rates of tubular reabsorption are exceeded, or even such that there is significant competition between the various components.[2274] The reabsorptive mechanism at low plasma levels is so effective that, on a diet containing 1 gm of protein per kg. of body weight per day, man excretes only a minute fraction of any of the ingested amino acids, the greatest renal loss occurring with histidine.[929, 1124, 1874]

CREATINE

Interest in the excretion of creatine is enhanced by the fact that this substance, as phosphocreatine, plays such an important role in the mechanism of skeletal muscle. It is accepted that creatine is an anabolic product synthesized and conserved for this specific end (muscle metabolism) in the same sense as glucose or protein is conserved. Creatine is synthesized from arginine (the amidine group), glycine (the sarcosine moiety), and the methyl group of methionine. For reasons unknown, it is slowly converted to creatinine, which is excreted. It can be confidently said that all urinary creatinine (exclusive of exogenous dietary creatinine and creatine) is derived from muscle creatine; apparently creatinine cannot be converted to creatine in the body. It should be noted that during cooking much of the creatine of meat is converted to creatinine and ingested as such.

Creatine normally predominates over creatinine in the urine of birds and reptiles,[727, 1046, 2215] Amphibia (unpubl. obs.), fresh-

water and marine teleosts,[872,1392,1402,1917,1920] and elasmobranchs.[2112] Conversely, creatinine commonly predominates over creatine in the urine of mammals,[727,1701] but creatine may appear in large quantities in the urine of herbivores and young mammals generally.[1036,1575,1927,1941]

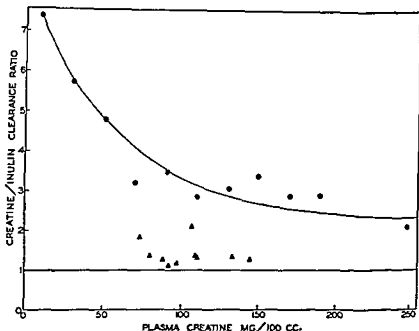


FIGURE 21. Creatine/inulin clearance ratio in the normal teleost, *Epinephalus morio* (dots), and after phlorizin (triangles), which blocks tubular excretion, in relation to plasma creatine concentration. Each dot represents the average of 10 observations; each triangle is a single observation. (Pitts[1626])

In man, creatine is a constant but variable component of the urine in both sexes from birth to puberty, although creatinuria is more marked in girls than boys after the first few years. After adolescence it disappears from the urine of man, but creatinuria recurs intermittently in women in relation to the ovarian cycle, and it reappears in old men and becomes more marked in women after the menopause. Creatinuria also occurs where there is disturbed carbohydrate metabolism, as in phosphorus or phlorizin intoxication, and in diabetes mellitus, starvation, acute denervation atrophy, and other conditions where skeletal muscle de-

struction occurs, and it is usually associated with hyperthyroidism, in which condition it disappears after the administration of iodine. Conversely, hypothyroidism in children is accompanied by a diminished creatine excretion. In myasthenia gravis, small oral doses are in great part excreted in the urine because of inadequate deposition in the muscles.

The examination of the normal creatine clearance is rendered difficult, as in the case of creatinine, by the lack of a specific analytical method. The normal plasma concentration of creatine is so small relative to the analytical error that reabsorption of endogenous creatine is difficult to examine accurately. Tierney and Peters [2079] have shown that creatine appears in the urine of normal males only when the plasma concentration exceeds 0.5 mg/100 cc. On the available evidence it may be inferred that this plasma chromogenic substance is creatine, that it is completely filtrable from plasma, and that it is completely reabsorbed at low plasma levels. It has been clearly demonstrated by Pitts [1621, 1622] and by Zierler, Folk, Magladery, and Lilienthal [2291] that, when the plasma level of creatine is raised, excretion is incomplete because of tubular reabsorption. The rate of reabsorption continues to increase at the highest filtered loads attainable, and the data do not indicate a maximal rate. Rather at high plasma levels the creatine/C_F clearance ratio tends to become constant at about 0.8 in both the dog and man *

Pitts [1620, 1621] has shown that creatine and amino acids are reabsorbed by the same tubular mechanism, when this mechanism is saturated with glycine, alanine, or glutamic acid, creatine reabsorption is blocked.† Since ingested creatine is in part stored in

* Tierney and Peters [2079] find that the apparent creatine clearance rises with rising serum concentration, but that it always remains lower than the endogenous creatinine clearance Since the latter bears an uncertain relation to the filtration rate in man, no conclusion can be reached from these experiments in regard to the relation between the creatine clearance and the filtration rate except to say that no creatine is excreted by the tubules

† Pitts says, 'These experiments should well disturb those groups of investigators who study precursors of creatine by feeding various amino acids and note only the elimination of excess creatine in the urine In fact the use of such a method of approach in any metabolic study cannot be too heartily condemned, for it neglects possible direct alterations in renal function.' A parallel situation is represented by the increased vitamin C excretion induced by various compounds (estradiol, etc) which interfere with its tubular reabsorption

the tissues or destroyed, fairly large doses must be administerec to normal animals before creatinuria occurs.

For unknown reasons, DCA and thyroid block creatine reabsorption in man and may bring the creatine/mannitol clearance ratio up to 1.0. Tubular reabsorption is decreased during puerperium, in thyroid disease, and in Cushing's disease, but the

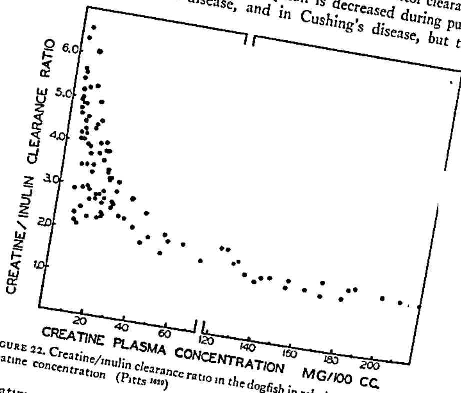


FIGURE 22. Creatine/inulin clearance ratio in the dogfish in relation to the plasma creatine concentration (Pitts [1029])

creatinuria accompanying the administration of methyltestoster one to man is unrelated to decreased tubular reabsorption.[2291, 229]

Phlorizin has no effect upon the creatine clearance in the dog at any plasma level,[1622] although prolonged phlorizinization leads to excessive protein destruction and hence to creatinuria.

In marked contrast to the case in dog and man, creatine is copiously excreted by the tubules of the aglomerular fish, the glomerular teleost, *Epinephalus morio* (fig. 21),[1026] and the glomerular dogfish (fig. 22).[1029] In the last, creatine Tm is about 60 mg/day per kg. Phlorizin blocks the tubular excretion of creatine in *E. morio*, but not in the dogfish, even

though the dose of phlorizin in the latter is sufficient to produce complete glucuresis.[1809] When both creatine and creatinine are administered to *E. morio*, the clearances of these two substances are not identical, the substance with the lower plasma level having the higher clearance.[1809]

GUANIDOACETIC ACID

At plasma levels of 0 20 to 0 23 mg/100 cc the guanidoacetic acid excretion is negligibly small The infusion of creatine sufficient to raise the plasma creatine level to 1.0 mg/100 cc. and to cause the appreciable excretion of creatine leads to a considerable increase in guanidoacetic acid excretion, implying a common mechanism of transport. However, guanidoacetic acid has no appreciable effect on the reabsorption of creatine [1901]

β-HYDROXYBUTYRIC ACID

Limited examination in the dog indicates that DL-β-hydroxybutyric acid has a maximal rate of tubular reabsorption between 2 and 3 mg/min per kg. of body weight. There is appreciable excretion at load/Tm ratios of 0.3.[2116] Accelerated excretion occurs in man at blood levels of 20 mg/100 cc. and over [1409]

LACTIC ACID

DL-Lactic acid is almost completely reabsorbed in the dog until the plasma concentration approaches 100 mg/100 cc At higher levels there appears to be a maximal reabsorptive rate which is not influenced by the proportions of L and D isomers in the filtrate, i e both isomers are handled by the same mechanism and the saturation load is independent of isomeric composition However, the L isomer is preferentially reabsorbed, the coefficient of reabsorption, D/L, being 0.68, the same value as the coefficient of utilization (0 65) in simultaneous experiments. Consequently a higher load of the D isomer than of the L isomer is required to effect saturation (This relationship was deduced from the relative composition of the plasma and urine and not by actual measurement.) Simultaneous loading of the tubules with glucose and lactic acid had no noticeable effect upon the reabsorption of either.[449]

Lactic acid excretion began in two subjects at a plasma concentration of 60 mg/100 cc. of whole blood, at lower concentrations the whole blood clearance ranged from 1 to 2 cc.[1449]

PHOSPHATE

Phosphate is important to the body in a number of ways: as calcium phosphate it is a major constituent of bone; in organic phos-

phate complexes it is important in energy transformations within cells and an essential component of many proteins and lipids; and, as the chief buffer of the urine, inorganic phosphate is indispensable in the maintenance of the acid-base balance.

Most of the urinary phosphate is in the inorganic form ($H_2PO_4^-$ + $HPO_4^=$) and it is believed that this is also true of the acid-soluble phosphate of the plasma. There appears to be a poorly ionized calcium-phosphate complex in the plasma, which in theory would be in equilibrium with free phosphate ions.[117] Of ionic plasma phosphate, about 80 per cent is present at pH 7.4 as $HPO_4^=$ and 20 per cent as $H_2PO_4^-$. All the plasma inorganic phosphate, however, is normally ultrafiltrable,* [828, 871, 1585, 1620, 1943, 2124, 2135, 2188] and, since the urine may be practically phosphate-free, either $H_2PO_4^-$ or $HPO_4^=$, or both, must be reabsorbed by the tubules.† We may think of phosphate as excreted in relation to the body's need, and view the $H_2PO_4^-/HPO_4^=$ ratio of the urine as an incidental consequence of the hydrogen ion concentration of this fluid.

The excretion of phosphate in the dog has been examined by Harrison and Harrison[922, 923] and in greater detail by Pitts and Alexander.[1635] Both groups of investigators agree that the capacity of the renal tubules to reabsorb phosphate is a sharply limited one.‡ Pitts and Alexander have shown that when the plasma level is normal or below normal, as it may be in fasting animals re-

* Harrison and Harrison[923] believe that there is appreciable binding on plasma protein.

† Phosphate is excreted by the tubles of the aglomerular fish, although it is uncertain whether the plasma precursor is organic or inorganic phosphate.[44, 14] Phosphate is also excreted by the tubules in the glomerular dogfish, *S. acanthias*, but again the evidence does not permit one to decide whether the plasma precursor is the inorganic or an organic form.[1944] There is no convincing evidence that phosphate is ever excreted by the tubules in mammals. Barclay, Cooke, and Kenney[73] have argued that, whereas phosphate is reabsorbed in the dog at low plasma levels, at high plasma levels it is excreted by the tubules; but no evidence to this effect is given in the report cited.

‡ Smith, Ollayos, and Winkler[1943] arrive at the contrary conclusion that there is no maximal rate of tubular reabsorption in the dog, but, as Pitts and Alexander point out, their experiments are complicated by rapid falls in plasma concentration and, in some experiments, by progressive marked reduction in filtration rate. The latter changes are so great and unprecedented as to vitiate the experimental results.

ceiving glucose, over 99 per cent of the filtered phosphate is reabsorbed and the clearance is practically 0.0. As the plasma level is raised, tubular reabsorption remains essentially complete until the load/Tm ratio reaches about 0.75, when urinary excretion begins (fig. 23). Tubular saturation is reached at a load/Tm ratio o

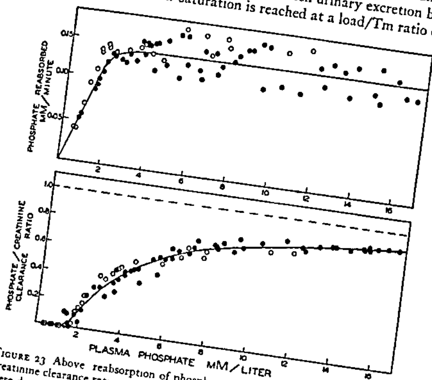


FIGURE 23 Above reabsorption of phosphate in two dogs Below phosphate/creatinine clearance ratio in relation to plasma phosphate concentration Curves were drawn free-hand (Pitts and Alexander [1044])

about 1.5. The maximal reabsorptive capacity in three dogs was 0.13, 0.14, and 0.18 mM/min. per sq. m. (These figures correspond to 0.11, 0.13, and 0 20 mM/100 cc. of glomerular filtrate when the dogs were on a mixed diet) Corresponding absolute figures on two dogs studied by Jahan and Pitts [1047] were about 0.079 and 0.074 mM., and 0.15 and 0.12 mM. in two dogs studied by Ayer, Schiess, nd Pitts.[46]

Harrison and Harrison [922] and Barclay and Kenney [46] claimed

that phosphate reabsorption is functionally related to the filtration rate, but Pitts and Alexander,[1626] and Ayer, Schiess, and Pitts [66] have shown that the maximal rate of phosphate reabsorption is constant for a given dog and independent of the filtration rate when that rate is varied over a range of nearly 100 per cent by altering the protein content of the diet (fig. 24).

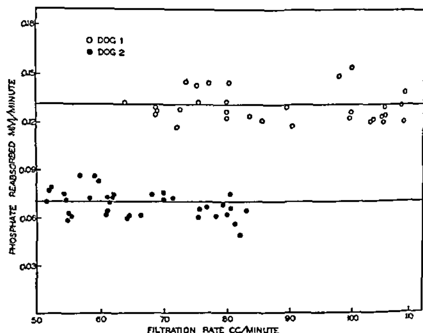


FIGURE 24. Experiments showing that the maximal rate of reabsorption of phosphate in the dog is independent of the filtration rate. The latter was varied by altering the protein content of the diet (Ayer, Schiess, and Pitts [66])

Apparently phosphate reabsorption shares a common element with the reabsorption of alanine and glycine, since elevation of the plasma level of these amino acids depresses phosphate reabsorption to about 35 per cent of its control value.[66] Under anabolic conditions the plasma phosphate concentration may be reduced by extrarenal removal to a point where the tubules are markedly unsaturated. During resting conditions on an adequate phosphate-containing diet, however, it is probable that the plasma concentration, and hence the filtered load, is just such as to saturate the tubules, and at such times the plasma concentration may be said

to be determined by glomerular-tubular balance, with due regard to any splay in the titration curve. Neither hydrochloric acidosis nor bicarbonate alkalosis affects phosphate Tm in the dog, as is shown in figure 23. Saturation of the tubules with phosphate has no effect on chloride reabsorption and, conversely, the infusion of sodium chloride, with marked elevation of plasma chloride concentration, has no immediate effect on phosphate Tm. The prolonged infusion of glucose markedly decreases phosphate Tm,[1635] but phosphate Tm decreases on the prolonged infusion of phosphate itself in both man (Michie, pers. com.) and dog;[1023] in the latter this effect is somehow related to potassium, and therefore the apparent specific interference by glucose may be an artifact. Michie's studies in man indicate that the parathyroid hormone may be involved in this phenomenon. Until these basic questions are resolved, changes in phosphate reabsorption during prolonged infusion cannot be accepted as a three-way mechanism (filtration-reabsorption-tubular excretion) of excretion.[81] Phlorizin blocks the reabsorption of glucose but not that of phosphate[1866] Indeed, phlorizin increases phosphate Tm by a small amount,[1635] indicating that, as measured in the normal animals, phosphate Tm is slightly depressed by the normal reabsorption of glucose. Whatever the common element in the reabsorption of glucose and phosphate it must be an early one, since the former is phlorizin-sensitive and the latter is not. Alternatively, it is possible that there may be competition on the basis of available energy; if the glucose reabsorptive mechanism is blocked by phlorizin, the energy originally diverted into these channels may become available for the reabsorption of phosphate.

Entirely similar results on man are reported by Schiess, Ayer, Lotspeich, and Pitts.[1781] Phosphate Tm in the one subject examined was 0.130 mM In man, however, the splay of the titration curve is increased during acidosis, so that appreciable excretion begins at lower plasma levels; the net effect is to increase the available buffer in the urine at plasma concentrations of 0.5 to 1 0 mM/liter (fig. 25). It is generally conceded that acidosis in man increases the excretion of phosphate; however, the increase is limited to the first few days, phosphate excretion diminishing thereafter as ammonia excretion increases. In addition to the

light change in the splay of the titration curve in the one subject reported above, this may reflect an increase in the urine/fecal excretion ratio in acidosis or the mobilization and loss of a limited store of labile body phosphate.

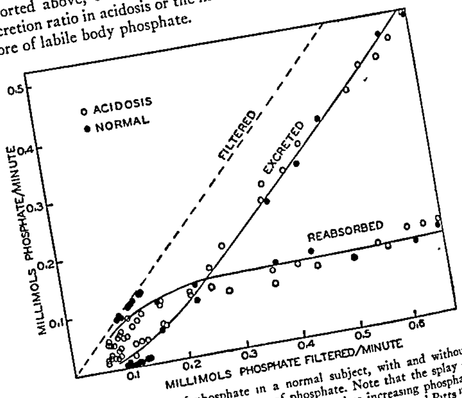


FIGURE 25. Excretion of phosphate in a normal subject, with and withou acidosis, in relation to rate of filtration of phosphate. Note that the splay the titration curve is slightly increased in acidosis, thus increasing phospha excretion at low plasma concentrations. (Schiess, Ayer, Lotspeich, and Pitts

Harrison and Harrison [923] report that the administration of tamin D to young dogs that had been fed a rachitogenic diet duced a marked increase in phosphate Tm, an effect demonstr within 24 hr. These investigators, from studies over a na range of plasma phosphate concentration, concluded that thyroid hormone depresses tubular reabsorption, but Fay, mann, and Buck [628] conclude from more extensive observatio normal, parathyroid treated and parathyroidectomized dog a lack or an excess of hormone had no demonstrable eff tubular reabsorption. This conclusion has been affirmed by

and Pitts [1067] from observations on normal dogs before treatment and some 16 hr. after treatment with the hormone, which would not reveal any transitory effect.[269] But Michie and McConnell (pers. com.) have observed that 200 units of parathyroid hormone, given intravenously to patients with hypoparathyroidism following thyroidectomy, had no effect on tubular reabsorption of phosphate within 3 hr. Phosphate excretion was increased because of a slight increase in filtration rate, tubular reabsorption remaining constant. In normal subjects, the hormone induced no changes in tubular reabsorption or in excretion, and Hogben and Bollman [1023] report that parathyroid extract has no effect on tubular reabsorption in the dog within 2 hr. of administration. However, in a preliminary note, Cargill and Witham [230] obtained decreased tubular reabsorption in normal subjects receiving parathyroid hormone, and believe that the effect is related to simultaneous glucose reabsorption.

The fact that the maximal reabsorptive capacity of the tubules for phosphate is relatively stable * and uninfluenced by marked changes in chloride excretion and in acidosis and alkalosis, indicates that phosphate is handled by the kidney in a specific manner and not merely as an indifferent electrolyte. The maintenance of a fairly constant plasma concentration is directed towards the many purposes which phosphate serves in the body. The stable tubular reabsorptive mechanism is such as to maintain a constant plasma level so long as the rate of phosphate production and the filtration rate remain constant. The utilization of urinary phosphate in the excretion of acid and conservation of base is incidental

* Ollayos and Winkler [1111] found that the rate of excretion of phosphate did not correlate with the plasma concentration at normal levels (1.0 to 1.5 mM/liter) in man. They point out that insulin and carbohydrate administration in diabetes causes a reduction in serum phosphate which is paralleled by a reduction in excretion, whereas in normal subjects not receiving insulin the ingestion of food frequently increases excretion without an increase in serum concentration. There is, moreover, a diurnal cycle in excretion which fails to parallel serum concentration. In view of Pitts and Alexander's observation that glucose and phosphate share a common reabsorptive mechanism, and that even the normal reabsorption of glucose decreases phosphate Tm, these variations may have an explanation in changes in glucose load. However, the evidence for the presence in plasma of an ultrafiltrable calcium-phosphate complex, which would in theory not be handled like inorganic phosphate, should not be overlooked.

and attributable to the circumstance that it is the major buffer present in urine, being the only buffer substance produced in the body in significant amounts which is excreted by this route.

Walker and Hudson[2135] found that, in *Necturus*, phosphate is reabsorbed in the proximal tubule, and presumably this is the case in mammals.

Nothing in the available data indicates whether the renal tubules reabsorb $H_2PO_4^-$ or $HPO_4^=$ or both. If reabsorption occurs in the proximal tubule, it is probably isohydrically from a tubular urine having the same pH as plasma (7.4), where the ratio $H_2PO_4^-/HPO_4^=$ is 0.25.

The normal excretion of phosphate is not increased during water diuresis,[932, 1067, 1555, 2213] or during osmotic diuresis induced by mannitol[2171] or urea.[1488] Phosphate excretion is increased in dogs by pitocin[692] and by the injection of large doses of the sodium salt of p-aminohippuric acid in man, the effect in general being related to the plasma concentration of the latter.[2174] (The injection of PAH and diodrast in large doses in man also leads to the transient acidification of the urine to pH 5.0 to 5.5.) (unpubl. obs.) Phosphate excretion is decreased by hypophysectomy.[271, 946]

Some investigators*[922, 923] lay great emphasis on the renal threshold as the determinant of plasma phosphate concentration. While in a sense this is true, plasma phosphate is equally determined by the rate of absorption from the gut and the equilibrium between circulating phosphate and intracellular or skeletal phosphate. Thus a change in plasma phosphate concentration is no indication *per se* of a parallel change in renal threshold. For example, the infusion of glucose lowers plasma phosphate and as a consequence diminishes phosphate excretion.[925, 1665] Similar effects are produced by hyperventilation,[886] while breathing carbon dioxide raises plasma phosphate and increases excretion.[885] These changes are indications of altered equilibria between phosphate stores and circulating phosphate rather than alterations in the renal mechanism

* Harrison and Harrison[923] maintain that the reabsorptive capacity of the tubules *for phosphate is decreased by acidosis, but in their* experiments the filtered phosphate rarely exceeded that reabsorbed by a significant amount, and it is probable that the tubules were not saturated. Under these conditions T will vary directly with the filtration rate. The data of Pitts and his coworkers indicate a difference between man and dog in this respect.

governing excretion. Presumably, the major effect of acidosis on phosphate excretion is of this character.

SULPHATE

Of notable interest in the history of studies on the excretion of sulphate are those of Mayrs,[1422] carried out in 1922. On the assumption that all metabolic waste products would be equally readily excreted by the kidneys, Mayrs studied the simultaneous U/P ratios of sulphate, creatinine, phosphate, and urea in anesthetized rabbits. He injected sulphate and phosphate, and sometimes urea and creatinine, in order to raise the plasma concentrations to determinable values and, under the limitations of analytical methods then available, he found that the U/P ratios of sulphate and phosphate were close to identity (1.06 to 1.19), and, in other experiments, so were the U/P ratios of sulphate and creatinine (0 95 to 1.25); he concluded that '. . . it requires a stretch of imagination to suppose that [these substances] are secreted independently of each other. It is simpler to assume that they are concentrated by removal of water (from the glomerular filtrate), and to account for possible slight differences in their concentration ratios by admitting that small quantities of "no-threshold" bodies may be absorbed.' The U/P ratio of urea, Mayrs found, was only some 35 to 50 per cent of the simultaneous sulphate or creatinine U/P ratio, and he concluded that the difference was attributable to tubular reabsorption. Calculating the rate of glomerular filtration from the plasma concentration and rate of excretion of sulphate, and deducting the quantity of urine excreted, he estimated the volume of water and the quantity of urea reabsorbed under various conditions and showed that, contrary to Cushny's theory, the composition of the reabsorbed fluid is not constant in respect to urea, but varies between wide limits and never reaches the existing concentration in the plasma. Subsequently, Mayrs and Watt [1423] measured the blood flow in the rabbit's kidney and, using sulphate excretion as a means of calculating the filtration rate, concluded that about 20 to 25 per cent of the plasma is filtered through the glomeruli.

Thus Mayrs was the first to adduce quantitative evidence in favor of the common mechanism, glomerular filtration, for the ex-

cretion of several substances, to estimate the filtration rate, to indicate that about 50 per cent of the filtered urea was reabsorbed, contrary to Cushny's theory, and to show that the composition of the reabsorbate is not always the same.

White,[2183,2184,2185] in studies in phlorizinized dogs, obtained practically identical U/P ratios for glucose and phosphate at high plasma levels of the latter, but failed to confirm Mayrs in the conclusion that, at high plasma levels of phosphate and sulphate, the U/P ratios of these substances are identical. Finding that the ratios were highly divergent when the plasma concentration of one substance was normal and the other was elevated, he concluded that urea, glucose, phosphate, and sulphate were all excreted in part by the tubules.

Poulsson[1663] reaffirmed the simple filtration of sulphate on the basis that the urinary concentration in man varied in proportion to the U/P ratio of creatinine, while Hayman and Johnston,[938] comparing the U/P ratio of sulphate and creatinine in man, inferred that if sulphate is filtered it must be extensively reabsorbed. Hayman and Johnston showed that, when the sulphate plasma level is elevated, the U/P ratio approaches but never quite equals that of creatinine. Cope[402] also demonstrated in man that the sulphate clearance at normal plasma levels is about 30 per cent of the creatinine clearance; rejecting the possibility of reabsorption of sulphate, he suggested that the filtration rate is equal to or somewhat less than the sulphate clearance and that additional sulphate and creatinine are excreted by the tubules. Macy,[1364] and Keith, Power and Peterson[1102] similarly showed that at normal plasma sulphate levels the sulphate clearance in man is always less than the creatinine clearance and usually less than the urea clearance, and White and Monaghan[2207] confirmed this relationship in dogs. In the observations of Keith *et al.* the sulphate clearance averaged 35.5 cc. and the urea clearance 72.2 cc, as compared with 89 5, 100 and 150 cc., respectively, for the xylose, sucrose, and creatinine clearances. Subsequently, Goudsmit, Power, and Bollman[822] showed that, in the dog, the sulphate clearance is normally about 8 per cent of the creatinine clearance, and that it increases on elevation of the plasma sulphate concentration and approaches the creatinine clearance asymptotically.* Under extreme

* Between 30 and 200 mg/100 cc. the sulphate/creatinine clearance ratio is apparently independent of whether the plasma concentration is rising or falling, but below 30 mg/100 cc. this ratio tends to be higher on a falling than on a rising curve. It is impossible from the published data to determine whether or not this discrepancy would be abolished by the application of an appropriate correction for delay time and dead space error, which the authors do not men-

conditions which lead to the animals' death * (325 and 353 mg. of sulphate per 100 cc of plasma) the clearance ratio rose slightly but not significantly above 1 0.

Goudsmit *et al.* concluded that sulphate is present in the glomerular filtrate in the same concentration as in the plasma, but that about 90 per cent is reabsorbed at normal plasma levels; on elevation of the plasma concentration, a (maximal) rate of tubular reabsorption of about 12 mg/100 cc. of filtrate would account for the clearance ratios. This interpretation is, however, rendered somewhat uncertain by the fact that the presumed maximal rate of reabsorption appeared to be lowered transiently by the injection or feeding of sulphate. The authors note that there is a reciprocal relation between plasma level and sulphate clearance in dog and man, in the former, the normal clearance is only 8 to 10 per cent of the filtration rate, and the normal plasma level averages 1.3 mM/liter; in man, the normal sulphate clearance averages 30 per cent of the sucrose clearance (or 25 per cent of the filtration rate) and the normal plasma level averages 0 4 mM/liter Thus the rate of excretion (UV) per 100 cc of filtrate is roughly the same in the two species

Bjering and Øllgaard [178] reported the normal sulphate clearance in man as 37 cc as compared to 71 cc. for urea and 148 cc for creatinine. On elevation of the plasma sulphate concentration, the clearance rose to 95 cc in one individual, and to 85 cc in a second (creatinine clearances of 137 and 124 respectively) They attributed the low clearance at low plasma levels to protein binding (75 per cent) of endogenous sulphate and, applying a correction of −0 8 to 0 9 mg/100 cc. to their data, obtained constant clearances of 99 and 91 cc (creatinine/sulphate clearance ratios of 1 36 and 1.38), and they called attention to the identity of these ratios with the average creatinine/inulin clearance ratio of 1 39 They concluded that, subject to correction for plasma binding, the sulphate clearance is at the level of glomerular filtration The correction made by Bjering and Øllgaard can be expected empirically to give a relatively constant clearance and to elevate the clearance to the asymptote (filtration rate), but this correction is unwarranted, since sulphate is not significantly bound by plasma protein. The observations of

tion. At normal plasma levels the sulphate clearance appears to increase with urine flow, but again it is not clear that variations in the plasma sulphate concentration may not account in part for the variation in clearance ratio.

* By slow plasmapheresis, Amberson *et al* [19] were able to obtain 960 mg. per cent of sulphate (100 mM/liter) in the plasma of cats, the chloride being reduced to 7 mM/liter

Hayman and Johnston[935] and of Goudsmit, Power, and Bollman[82] show that endogenous sulphate is completely ultrafiltrable in man and dog.

More recently, Schwartz, Smith, and Winkler[1806] confirmed the fact that at low plasma levels the sulphate clearance is lower than at high plasma levels, the clearance increasing with plasma level. They failed, however, to confirm the observation that the sulphate/creatinine clearance ratio approaches 1.0 as a limiting value, and in some of their experiments this ratio decreased as the plasma sulphate level increased. They also stated that there is no evidence of a maximal rate of tubular reabsorption. They found that the simultaneous administration of sodium chloride increased the sulphate clearance, while the administration of sodium sulphate in the doses used by them decreased the excretion of chloride. Sulphate excretion was, in the main, independent of the associated cation (potassium and magnesium). The comparisons of Schwartz *et al.* were, however, made in different experiments, and observations were made during rapidly falling plasma sulphate concentrations, so that it is difficult to interpret the resulting sulphate clearances.

Schou[1799] found that during osmotic diuresis induced by the infusion of hypertonic sodium sulphate into rabbits, sulphate reabsorption apparently reached zero. However, under conditions of maximal diuresis (creatinine U/P ratio of 1.5 to 3.0), sulphate excretion sometimes exceeded the filtered quantity by as much as 15 per cent, a fact which he attributed to the compounding of errors in four analyses, including a rapidly changing plasma sulphate concentration. Since the sulphate U/P ratio was always greater than 1.0, he expressed the belief that sulphate reabsorption is never greater than what might be explained by a passive diffusion process, but the design of the experiments was not such as to afford reliable information on this point.

Thus, sulphate has been foremost in the minds of investigators working with the comparative clearance method. The description given by Goudsmit *et al.* was supported by most of the data, and indicates that the low clearance at low plasma sulphate levels is attributable to tubular reabsorption, a process possibly characterized, as they suggest, by a maximal rate.

Lotspeich's[1273] studies of sulphate excretion in the dog show that at normal plasma concentrations and normal filtration rate, sulphate is almost quantitatively reabsorbed. With any slight increase in filtered load, the reabsorptive capacity is rapidly exceeded, i.e. the threshold is very sharp (fig. 26). The rate of re-

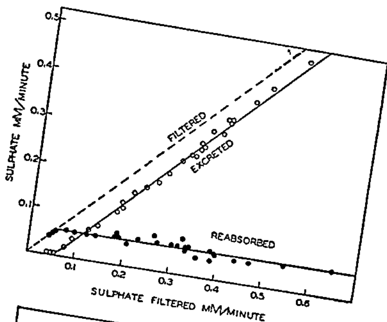


FIGURE 26 Above excretion of inorganic sulphate. Below: sulphate/creatinine clearance ratio in the dog in relation to the quantity filtered. (Lotspeich

absorption is constant from plasma concentrations of 1.2 to 20 mM/liter (load/Tm ratios of 1.0 to 12). Lotspeich warrantably infers that sulphate is reabsorbed by an active process, and defines a maximal rate of reabsorption (sulphate Tm).

Sulphate Tm had a value in 2 dogs of about 0.166 and 0.135 mM/100 cc. of glomerular filtrate. Since plasma sulphate is derived only from metabolic production, without significant storage in any organ, the plasma concentration is determined at any moment by the balance between the filtration rate and sulphate Tm. *This is unlike the situation with glucose, amino acids, etc*, where the plasma concentration is maintained by extrarenal regulation at levels too low to effect tubular saturation. A similar situation exists in the excretion of endogenous creatinine chromogen in some individuals, and is approached but not equalled in the excretion of creatine and phosphate. Plasma sulphate can be expected to rise as glomerular filtration is reduced, as noted by Goudsmit and Keith,[821] but it remains susceptible to variation as a result of variation in protein metabolism.

Under normal conditions, sulphate reabsorption is independent of chloride and phosphate load. Decreased reabsorption is associated with hypertonic sodium chloride diuresis, but not with the increased sodium and chloride reabsorption that accompany an increase in filtration rate; hence it appears that the former is related to the disturbances of osmotic diuresis.

Sulphate is ordinarily considered to be an inert waste product, but the studies of Dziewiatkowski [667] have shown that exogenous sulphate can be used to form the ethereal sulphate fraction in the urine, the evidence indicating that if sulphur from other sources is used for this purpose it is first converted to sulphate before being conjugated with phenols. This observation gives some meaning to the conservation, by active tubular reabsorption, of this anion.

URIC ACID

For a century after the discovery of uric acid by Scheele (1776), this compound occupied an important place in biochemical research. It has been of special interest because it is *frequently the* material of renal calculi and gouty deposits, and because of the peculiarities of its metabolism.

In the mammals, waste nitrogen is excreted chiefly as ure
uric acid appears in the urine only in consequence of the me
lism of the purine bases which are constituents of ingested nu
proteins and of endogenous metabolism. The nucleic acids are
graded to nucleotides and ultimately to the purine bases, wh
are then converted to uric acid In most mammals the uric aci
then oxidized to allantoin, giving a low uric acid/allantoin ra
in the urine; but in man, the anthropoid apes, and the New Wor
monkeys,[1701] and in the Dalmatian coach hound, a great fractio
of the uric acid is excreted as such. Although the Dalmatian houn
converts uric acid to allantoin less readily than other breeds, this
circumstance seems to play a minor role in determining the differences in excretion. In the Dalmatian, the uric acid clearance is identical with the filtration rate, consequently the compound is rapidly excreted with minimal oxidation to allantoin.[709] In other breeds, on the contrary, the uric acid clearance is only some 25 per cent of the filtration rate, probably because of tubular reabsorption (*vide infra*), and this slower rate of excretion permits a greater fraction to be oxidized. In man, however, the uric acid clearance is also low (6 per cent of the filtration rate), and here one must look to differences in the velocity of oxidation to explain the low uric acid/allantoin ratio. The high uric acid/allantoin ratio in the Dalmatian is a genetic character following the Mendelian law and correlating with spottiness

Previous determinations of plasma uric acid and of uric acid clearances are open to question because of the non-specificity of the older colorimetric methods Bonsnes, Dill, and Dana [209] record having a bibliography of 280 titles of papers dealing with the quantitative determination of this substance. Blauch and Koch [111] have introduced an enzymatic method, which has been further modified by Bulger and Johns,[290] this last modification being, presumably at least, better than any of the other 280 methods.

Brøchner-Mortensen [344, 117] reported uric acid clearances in normal men, fasting or on a purine-free diet, of 6.9 cc. at urine flows above 1.0 to 2 0 cc.; in simultaneous determinations the uric acid/urea clearance ratio averaged 0.10, the uric acid/exogenous creatinine clearance ratio 0.06 The use of a more specific plasma uric acid method would probably have doubled these figures.[209]

This author [256] reported no significant difference in the uric acid clearance in normal and gouty subjects. *The clearances tended to* decrease at urine flows below 1 cc., but *since the urine samples* were not collected by catheter the significance of this decrease is uncertain.[254] Coombs, Pecora, Thorogood, Consolazio, and Talbott,[400] using the Benedict-Behr method, report the uric acid and inulin clearances as averaging, respectively, 11.5 and 113 cc. in 8 subjects without gout or renal disease, and 6.5 and 68 cc. in 9 subjects with gout. Talbott [2041] reports these figures as ranging from 6 to 12 cc. for urate and 100 to 140 cc. for inulin in control subjects, and 4 to 11 cc. for urate and 12 to 130 cc. for inulin in patients with gout. *It is clear from Talbott's data that many gouty patients* have severe renal impairment (21 out of 27 had inulin *clearances* below 100 cc.) but it is not established that this is attributable to gout *per se*.* There was no difference in the range or average of the urate clearances in Talbott's gouty subjects (10 cc.) and in those without gout who were studied by Coombs *et al.*,† [400] and it is generally agreed that the tendency for uric acid to accumulate in the tissues in gout is not referable to deficient renal excretion.[25]

At an average plasma concentration of 6.26 mg/100 cc. of 'true' uric acid, the urate/inulin clearance ratio averages 0.083; at 10.06 *mg/100 cc. this ratio averages* 0.095.[2266] *The normal* true urate clearance in man may therefore be taken as about 12 cc. The non-urate chromogen in plasma, as determined by Bulger and Johns' method, consists largely of chemically uncharacterized purine metabolites that are cleared at about the same rate in man as is true uric acid at low plasma levels.[2265]

Berglund and Frisk [126] assumed that the uric acid clearance deficit was attributable to the circumstance that only a small fraction of the plasma uric acid is filtrable. However, when examined by customary ultrafiltration procedures using collodion, cellophane, or other semi-permeable membranes, the filtrable fraction is variously reported as 70 to 100 per cent, a figure which varies between species and between

* Uric acid salts injected intravenously have a very toxic action on the kidneys [illegible] large quantities [844] and the kidneys may be [illegible] asma urate levels in normal subjects, and the tendency to maintain a high plasma level of urate appears to be a genetic phenomenon.[1954,1990]

different individuals. (Berliner, pers. com.)[8,18,24,214,254,487,772,1424,2267] Levine and his coworkers[1278,2267] have argued that the clearance deficit is attributable to the circumstance that much of the uric acid in plasma exists in the form of non-filtrable polymeric urate complexes, and that substances which increase the excretion of uric acid (uricosuric agents) do so by increasing the filtrable moiety The arguments leading to this conclusion are as follows: a relatively small quantity of uric acid is present in cerebrospinal fluid, indicating lack of diffusibility on the part of the plasma urate. Within 12 to 24 hr. after ureteral ligation in the chicken, the average plasma total urate chromogen increased from 5.8 mg/100 cc, of which 86 per cent was true uric acid, to 304 mg/100 cc. of which 93 per cent was true urate. In normal chickens, 71 per cent of the plasma true urate was ultrafiltrable through cellophane, while 82 per cent was ultrafiltrable in the azotemic chickens When plasma or ultrafiltrates are refrigerated a heavy flocculent precipitate of urate forms, and fresh ultrafiltrate from both normal and azotemic chickens presents a Tyndall phenomenon which is greatly enhanced in the latter, indicating the presence of colloidal material Since the true solubility of urate in plasma water is of the order of 23 mg/100 cc, it follows that less than 10 per cent of the true urate in the azotemic ultrafiltrate is in true solution, the rest consisting of an ultrafiltrable polymer which passes readily into the colloidal state In the plasma, an additional moiety (some 29 per cent of true urate in normal plasma and 18 per cent in azotemic plasma) is alleged by these authors to be bound on plasma protein and thus rendered unavailable for filtration These investigators believe that the glomerular membrane is permeable to the ultrafiltrable polymeric urate, and that both the protein-bound and colloidal-polymeric forms may become available for tubular excretion in the chicken as the plasma concentration of true uric acid is reduced by diffusion into the renal nterstitial fluid They argue that analogous conditions may obtain at ormal urate levels in man, the presence of protein-bound and colloidal ate accounting for the low clearance value Hence they[2284] suggest at uricosuric agents increase the excretion of uric acid by increasing ultrafiltrable fraction and not by reducing tubular reabsorption. The interpretation advanced by Wolfson and his coworkers cannot ccepted as established Byers and Friedman,[308] from a comparative y of the distribution of urate between plasma and cerebrospinal in the non-Dalmatian and Dalmatian dog, conclude that the l-brain barrier is selectively discriminatory against the entrance th allantoin and uric acid, and that the low concentration of urate cerebrospinal fluid is not attributable to polymerization. They

advance other lines of evidence that plasma urate is essentially all ultrafiltrable.

In subjects with severe renal disease [400] the uric acid/inulin clearance ratio may rise to 0.70 to 0 88 and it is difficult to see why renal disease would affect either the polymerization or protein binding of uric acid in the plasma. It is also difficult to believe that uric acid would poly-

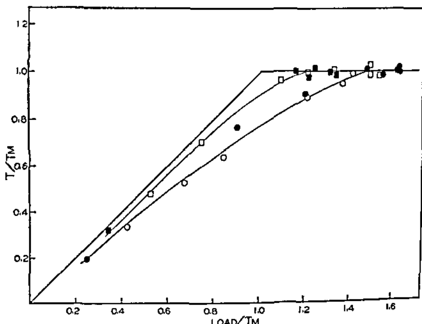


FIGURE 27. Excretion of uric acid in 3 normal subjects in relation to filtered load Note the marked splay in the titration curve (Berliner, Kennedy, Hilton, and Yu, pers com.)

merize in the plasma of the common dog and not in the plasma of the Dalmatian hound, or that sorbitol would decrease polymerization when mannitol does not. The demonstration by Friedman and Byers [705] that salicylate increases the uric acid/creatinine clearance ratio in the common dog but not in the Dalmatian hound, in which this ratio is *normally 1.0, is further evidence that the clearance deficit* is largely if not entirely attributable to tubular reabsorption.

Recent studies of Berliner, Kennedy, Hilton, and Yu (pers. com.) reaffirm the complete filtrability of uric acid from human plasma and demonstrate that there is an apparent maximal rate

of reabsorption in man, having a value of about 15 mg/min. (11.8 mg/min. per 100 cc. of glomerular filtrate). This value is so high that saturation almost certainly never occurs under physiological conditions. There is considerable splay in the titration curve, appreciable excretion occurring at load/Tm ratios as low as 0.5, while a load/Tm ratio of 1.25 to 1.50 is required to effect saturation. The titration curve in two individuals proved to be reproducible, and the authors believe that the splay in this curve reflects the kinetics of reaction in the transport system rather than disparity in glomerular-tubular balance (fig. 27).

In view of the non-specificity of the uric acid method, it is impossible to interpret the earlier data on uric acid clearances reported by Brøchner-Mortensen[333] after feeding nucleoprotein or purines. Grabfield and his coworkers,[332 333] in studies of the uricosuric effect of cinchophen, assert that unilateral renal denervation abolishes this uricosuric effect in both kidneys. The observations are, however, not controlled with respect to renal dynamics or postoperative metabolic disturbances of lymphoid and other tissues rich in uric acid precursors, and it cannot be accepted as proved that denervation of the kidney has any specific effect on the excretion of uric acid.

URIC ACID EXCRETION IN THE CHICKEN

The discovery that uric acid is present in large amounts in the excrement of birds was made by Fourcroy and Vauquelin (1811) shortly after Scheele's (1779) isolation of this compound from urinary calculi. It is now recognized that uric acid is a major nitrogenous product of protein metabolism in the insects, arid-living reptiles, and birds, a circumstance which has been interpreted as a biochemical adaptation to arid terrestrial life, for the properties of this substance are such that it can be excreted with a minimum of water.[1924,1931]

In view of the importance of uric acid in the metabolism of the birds, the mechanism of its excretion is a matter of considerable interest. Uric acid constitutes some 60 per cent of the total nitrogen in the ureteral urine of the chicken, the remaining nitrogen being mostly in the form of ammonia, creatine, and small quantities of urea (the normal urea content of chicken plasma ranges from 0.0 to 1.7 mg/100 cc[1044,1039]). In arid-living snakes the urine may take the form of dry concretions, of which uric acid composes 63 to 67 per cent of nitrogenous material, the rest consisting of ammonia and uncharacterized nitrogen. Urea, creatinine, and creatine are nearly or completely absent.[1117 1118]

Mayrs [1424] early suggested that uric acid is excreted by the tubules of the chicken, since he found that the (ureteral) U/P ratio was considerably greater than the simultaneous U/P ratios of phosphate and sulphate. A little later, Gibbs [772] showed that the concentration in the (ureteral) urine may reach such *extraordinary values as 21,600 mg/100* cc., and the U/P ratio, 3,110. Marshall [1394] has shown that the uric acid

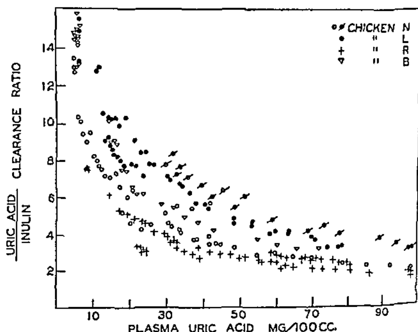
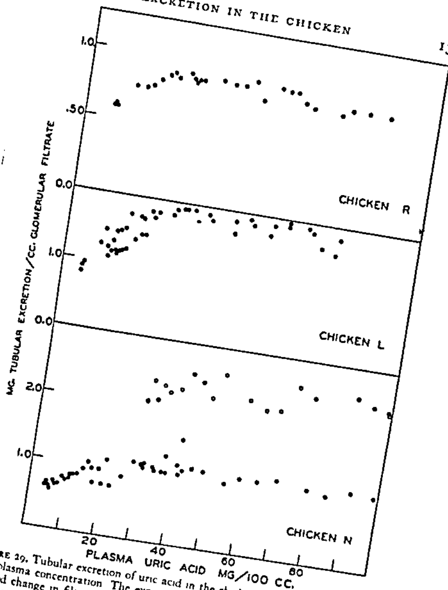


FIGURE 28 *Uric acid/inulin clearance ratio in the chicken in relation to uric* acid plasma concentration (Shannon [1856])

clearance in the phlorizinized chicken and iguana considerably exceeds *the glucose clearance.*

Shannon's [1856] studies of the chicken show that at normal plasma uric acid concentrations, the uric acid/inulin clearance ratio ranges from 7 5 to 15 8, indicating that 87 to 93 per cent of the uric acid is excreted by the tubules. As the plasma uric acid level is raised, this ratio is depressed (owing to reduction in the uric acid clearance) until at plasma levels of 100 mg/100 cc it has a value of 1.8 to 3.2 (fig. 28). Tubular excretion (T) increases with increasing plasma level until the latter has a value of 20 to 30 mg per cent, when it reaches an apparent maximum (Tm). At normal plasma levels T is 50 per cent or more of Tm (fig 29).



GURE 29. Tubular excretion of uric acid in the chicken in relation to the uric d plasma concentration The experiments included in this chart showed no rked change in filtration rate, but the data have been corrected to 100 cc. ltrate to eliminate technical errors. Although the data at the left represent ervations at normal plasma uric acid concentrations, the rate of tubular etion is already 50 per cent of the maximal rate Chicken N on 1 occasion ed an abnormally low filtration rate (circles) by about 60 per cent. (Shan-on)

Recalling that in birds the renal tubules receive an independent supply of blood by way of the renal-portal system, it is interesting to note that Tm may remain constant despite marked changes in the filtration rate.

In the pigeon, the formation of uric acid proceeds by the binding of ammonia in the liver to form hypoxanthine, which is then oxidized by xanthine oxidase in the kidneys as well as in other organs [570] to uric acid, and it may be that in birds urinary uric acid is a true renal metabolite in the sense in which ammonia is formed by the renal tubules in the mammals. This circumstance would not preclude tubular excretion of preformed uric acid in the ordinary sense.

It appears that after excretion into the tubular urine, changes in urine composition (water reabsorption, acidification, reabsorption of bases, etc.) lead to the formation of supersaturated uric acid solutions and ultimately to the formation of colloidal solutions and to precipitation of solid uric acid. In this process the uric acid ceases to be active osmotically, and its separation from solution liberates water for isosmotic reabsorption The milky ureteral urine, containing 0 6 to 3 per cent uric acid,[928, 1151] is passed into the cloaca and, under certain conditions *at least, is regurgitated into the rectum where more water may* be reabsorbed, the uric acid being excreted admixed with feces almost as a thick paste. Regurgitation into the rectum apparently does not occur during water or saline diuresis The rectum and cloaca are, however, incapable of doing osmotic work.*

The glomeruli in birds and reptiles are degenerate, the capillary tuft consisting frequently of four short capillary loops.[1406] The rate of glomerular filtration in the chicken is relatively small, averaging 1.22 cc/min during normal hydration, 2.19 cc. throughout the post-diuretic period, and 0.6 cc. during water deprivation (the last figure corresponds to about 6 cc/min. per sq. m., as contrasted with 84 cc. in the dog).[1151, 1025, 1556] This filtration rate would be wholly inadequate in the absence of tubular excretion to maintain the animal in nitrogen equilibrium without elevation of the plasma uric acid level *some 15- to 30-fold above normally* observed values. Alternatively, an adequate increase in filtration rate would entail a corresponding increase in the reabsorptive activities of [illegible] and, if water is to be conserved, a substantial [illegible] Since [illegible] od,[1151] [illegible] th an [illegible]

* Hart and Essex [538] present evidence that salt as well as water is reabsorbed in the rectum.

excessive filtration rate and excessive osmotic work. The normal water intake of the chicken ranges from 50 to 250 cc/day, the urine flow from 50 to 180 cc.[925,933] The manipulation of the bird in preparing it for experimental observation frequently produces a transient diuresis, and many urine flow figures are excessively high for this reason.

The data indicate that 1 gm of urinary nitrogen in the chicken requires only about 10 cc of water for its excretion. This figure in the alligator is 330 to 500 cc., and in the terrestrial semi-aquatic turtles, 250 to 2500 cc. In man (because the urine can be markedly hypertonic) each gm of nitrogen is normally contained in 130 cc. of water, the minimal figure being 40 to 60 cc. The mammal that is probably capable of excreting nitrogen in highest concentration is the desert rat, *Dipodomys*, the urine of which under extreme water deprivation may contain 22.1 gm/100 cc., or about 10 cc. of water per gm of nitrogen. Here again, this water economy is accomplished by hypertonic reabsorption in the renal tubules. Δ in *Dipodomys* urine is estimated to reach −10.4° C.; in the seal Δ may reach −4.0° C., in the dog −3.0° C or more, in man, −2.6° C., while in the chicken it does not exceed −1.0° C. Through the uric acid habitus the bird accomplishes equal water economy without doing any substantial osmotic work.

The uric acid habitus of birds and reptiles in relation to evolution, climate, and habitat have been discussed elsewhere.[1026,1031] In aquatic turtles, urinary nitrogen is largely urea and ammonia, but in arid terrestrial tortoises (*Testudo graeca* and *T elegans*) uric acid predominates over all other nitrogenous constituents[1455]

URICOSURIC AGENTS

Many substances are known that transiently increase the rate of uric acid excretion in man and rats: *cinchophen*,[400,1405] *salyrgan*,[400] *salicylate*,[708,1408,2041] *diodrast*,[309,2041] *carinamide*,[2284] *renin*,[1778] *glycine*,[104] *phenol red*,[2041] *acetylsalicylic acid*,[1133,1408] sorbitol,[2284] acetanilide, o-aminobenzoic acid, caffeine, metanilic acid, phenacetin, sulfanilic acid, adrenalin, theophylline,[1408] aminophylline,[128] adrenal cortical extract,[706] the italicized substances having been shown to increase the urate clearance relative to the filtration rate. Diodrast at plasma levels of 1 mg iodine per 100 cc. increases the uric acid clearance in man 2- or 3-fold, and at 25 to 40 mg. iodine per 100 cc. the clearance in some individuals may rise to the filtration rate.

Mannitol, inulin, creatinine, benzoate, hippurate, p-aminohippurate, and pitressin in moderate doses are without uricosuric effect,[2041] as is colchicine,[400] once widely used in the treatment of gout. But the

occurred in all dogs before maximal anemia had developed, and reabsorption tended to return to normal after cessation of treatment when anemia was still present Hence it does not appear that anemia is responsible for the phenomenon.

The splay in the vitamin C titration curve may reflect variation in the filtration rate/reabsorptive capacity ratio in individual nephrons, or it may reflect an intrinsic characteristic of the reabsorptive system whereby the efficiency with which the vitamin is removed from the tubular urine, even below the level of saturation, decreases as its concentration in the urine is increased. Selkurt *et al.* conclude that a final choice between these alternatives cannot be made from the presen evidence However, the fact that there is no large change in the filtratio rate suggests that estradiol increases the splay in the titration curve by altering the kinetics of the reabsorptive process rather than by altering the filtration rate/reabsorptive capacity ratio in individual nephrons This inference is supported by the fact that Tm is unchanged by treatment, although a greater load/Tm ratio is required to effect saturation

Since estradiol is known to increase the excretion of sodium chloride and potassium chloride, Selkurt and Houck [1826] examined the effects of infusing these electrolytes on vitamin C reabsorption. Control experiments in which creatinine and vitamin C were infused demonstrated that variations in apparent Tm were slight from period to period, relative to the average of all values for Tm ($\sigma/M = 0.15$) The prolonged infusion of mannitol in sufficient amounts to produce osmotic diuresis had no effect on Tm.

The continuous infusion of sodium chloride (6 per cent at 1.1 cc. following an average priming dose of 4.5 gm. of sodium chloride in 13 to 19 kg. dogs) depressed vitamin C Tm to 48 per cent of the control value after 20 min., to 37 per cent after 31.5 min. and to 36 per cent after 44 min. The sodium chloride increased the filtration rate by 12 per cent. The injection of 19 to 24 cc. of 10 per cent potassium chloride during an interval of 10 min. depressed vitamin C Tm to 58 per cent of normal 6.7 min. after the beginning of the infusion, and to 36 per cen at 16 min., after which Tm returned to normal or slightly above Th potassium chloride increased the filtration rate by 16.5 per cent and the PAH clearance by 13.6 per cent. It is concluded that sodium chloride and potassium chloride decrease vitamin C Tm by some tubular action other than osmotic diuresis, since mannitol has no such effect.

Selkurt [1820] has further shown that, when the excretory mechanism of the tubules is saturated with p-aminohippuric acid (PAH), the reabsorption of vitamin C is immediately blocked, but recovers gradually despite

continued PAH saturation.* PAH excretion at rates less than maxim(10 to 30 per cent of Tm_{PAH}) have no effect on vitamin C Tm. Change in filtration rate are excluded as a possible cause of the decreased reabsorption.

Saturation of the renal tubules by glucose in Selkurt's hands also transiently blocked the reabsorption of the vitamin, partial recovery occurring even though glucose saturation was maintained.† Constancy of the filtration rate and of glucose Tm excludes the interference of vascular effects. Although glucose reabsorption and PAH excretion offer only slight mutual interference, the depressant effects of glucose and PAH on vitamin C reabsorption are qualitatively additive. Phlorizin appears to impair but not block completely the reabsorption of vitamin C in the rabbit.[1608]

It appears that vitamin C reabsorption is linked in some way with tubular reabsorption (glucose) and tubular excretion (PAH) of other substances, but, since glucose reabsorption and PAH excretion do not occupy a common transfer mechanism, the linkage is probably not a matter of competition for a specific cellular component, but rather competition for the energy necessary for tubular transfer, or attributable to entirely secondary factors. The fact that, despite reduction of vitamin C reabsorptive capacity to zero or nearly so by all of the above-mentioned procedures, considerable recovery occurs in the face of continued administration of the depressing agent argues in favor of the last interpretation.

PANTOTHENIC ACID

Wright, Beyer, Skeggs, Russo, and Patch,[2271] using a microbiological assay method, find that, at normal plasma concentrations (0.10 to 0.32 γ/cc.), pantothenic acid is non-dialyzable at pH 7.4. On the addition to the plasma of 2 γ/cc., the added pantothenate, when dialyzed against 0.9 per cent saline, is quantitatively removed, and, when such fortified plasma is equilibrated with buffer having the same pantothenate content, the added pantothenate is approximately equally distributed between the plasma and the

* Under these conditions in man the urine becomes maximally acid for a short time.

† The effect of glucose is here in contradiction with the negative results reported by Ralli *et al.* and Sherry *et al.*, a difficulty which may be resolved by the fact that these investigators allowed a considerable period to elapse after injecting glucose and before making further observations on vitamin excretion, thus allowing the vitamin reabsorptive mechanism to recover.

dialysate. It appears that the non-diffusibility of 'endogeno pantothenate' cannot be attributed to reversible adsorption (plasma protein, since exogenous pantothenate is not so absorbe but the existence of this non-diffusible blank must be taken int account in calculating the exogenous clearance.

Wright *et al.* find that the clearance of 'endogenous pantothenate' at normal plasma levels in the dog is of a very low order, 0.2 to 0.5 cc. However, when the plasma concentration is increased by the oral or intravenous administration of the vitamin to about 0.5 γ/cc., the clearance rises abruptly and at plasma concentrations above 1.0 γ/cc., the pantothenate/creatinine clearance rati equals 1.0. It is concluded that exogenous pantothenate is excreted by filtration without tubular reabsorption, the low clearances at plasma concentrations below 1.0 γ/cc. being artificially reduced by the inclusion in the plasma term of the relatively large fraction of non-diffusible and therefore non-filtrable endogenous material.*

* Examination of the data indicate to the writer that a small systematic negative error in the recovery of plasma pantothenate would bring the behavior of the compound in line with vitamin C and creatine, compounds with small Tm values. That such an error may exist is indicated by the tendency for the pantothenate/creatinine clearance ratios to exceed 1.0 at high pantothenate plasma levels. This possible error does not necessarily have any relation to the presence of non-filtrable endogenous material in the plasma.

CHAPTER VI

Clearances Involving Tubular Excretion

A brief enumeration of substances that have been demonstrated to be excreted by the tubules will serve as a convenient preview.

Phenol red is excreted by the tubules in all animals examined: the aglomerular fishes, *Lophius piscatorius* and *Opsanus tau*,[1336] the frog,[130 475 1339] the dogfish,[1365] the chicken,[1329] the dog,[1392 1407 1847, 1873] and man.[800]

Creatinine (exogenous) is excreted by the aglomerular and glomerular tubules of the fishes,[891 876 1402, 1403 1625 1844 1844 1855, 1860] and by the glomerular tubules of the chicken,[1865] the anthropoid apes, (Houck, pers. com.)[1020] and man.[1346]

Creatinine (exogenous) is excreted *without* tubular excretion or reabsorption in the frog,[874] turtle,[891] dog,[1721, 1846, 1849 2093] sheep,[1381] rabbit,[1090] seal,[1327] and cat[741] (and probably the rat[703]).

Creatine is excreted by the aglomerular and glomerular tubules of the fishes,[1402 1626] but it is reabsorbed by the tubules in the dog and man.[1821]

Urea is excreted by the tubules of some fishes[1403] and of the frog,[1306, 1309 2132] but not in *Necturus*.[2131]

(Urea is *passively* reabsorbed by the tubules in the chicken,[1839] rabbit,[1090] dog,[1840] and man[848 1005])

(Urea is *actively* reabsorbed by the tubules in the entire Subclass Elasmobranchii (sharks, rays, skates, and chimerae), in which it serves a special role in the regulation of osmotic pressure.[1026])

Uric acid is excreted by the tubules in the chicken [1886] and reptiles.[1894]

(Uric acid is reabsorbed by the tubules in man (ch. v).)

In addition, it has been demonstrated that the tubules of the man (or dog) kidney excrete other phenol sulphonephthalein derivatives (unpubl. obs.), hippuric acid, and various hippuric acid derivatives, including hippuran and p-aminohippuric acid, as well as other conjugated aromatic acids such as cinnamoylglycine and phenaceturic acid, certain pyridone derivatives such as diodrast and N-pyridone acetic acid, penicillin and various acetylated sulfonamide derivatives. The fact that most of these substances are foreign to the body does not in the least diminish their physiological importance, for not only have they afforded valuable information on the mechanism of tubular excretion but many of them are related to non-metabolizable aromatic residues, such as hippuric acid, which normally occur in blood and urine and tl effective excretion of which may be important.

PRINCIPLES OF TUBULAR EXCRETION

Where the clearance of any substance, X, which is not synthesized by the kidneys is greater than the simultaneous inulin clearance in man (or creatinine clearance in the dog), i.e. when the X/inulin (or creatinine) clearance ratio is greater than 1.0, it may be accepted that X is excreted by the tubules in addition to being filtered through the glomeruli.

PROTEIN BINDING

As previously noted, many, if not most, weak electrolytes are bound by plasma albumin, a circumstance which reduces their availability for filtration, since the glomerular filtrate will contain the substance in the same concentration as it is present in the unbound (or free) state in the plasma water. If the plasma concentration of X is indicated by P_x, the unbound fraction by F, the water content of the plasma by W, and the filtration rate by C_F,

then the rate of filtration * of X in mg/min. will be

(1) $$P_xFWC_F$$

Protein binding, although it may somewhat retard diffusion from the peritubular capillaries into the interstitial fluid, will not otherwise render the substance unavailable for tubular excretion because as fast as the concentration in the interstitial fluid is reduced by abstraction into the tubules, more of the substance will diffuse from the capillaries, reducing the plasma concentration and thereby promoting the dissociation of the protein-X complex; the combination with protein being rapidly reversible, in principle all the substance contained within the plasma may (and actually does) dissociate and escape by diffusion before the blood emerges from the peritubular capillaries.

If removal is complete, the total rate of excretion (U_xV) divided by the plasma concentration (P_x), or the clearance of X, will be equal to the volume of plasma perfusing the glomeruli and tubules per unit time. No substance not synthesized by the kidneys can have a clearance greater than the renal plasma flow. The clearance will be less than the renal plasma flow if renal extraction is for any reason incomplete.

The possible values of renal clearances are illustrated in figure 6.

The plasma extraction ratio,† E, is the fraction removed between the renal artery (A) and renal vein (V), i.e. $(A - V)/A$. For any substance (regardless of tubular reabsorption or tubular excretion) the clearance, C_x, divided by E_x must be equal to the

* W appears in equation 1 because F refers the concentration in the water of the ultrafiltrate, P_f, to that in whole plasma, P. P_f is directly determined and is properly related to P_w, where $P_w = P/W$, W being the plasma water content. The ratio P_f/P_w is determined by the plasma concentration of albumin and the specific adsorbability of X, and the relations between the concentration of X and concentration of albumin can be generalized in an exponential equation or in a nomogram such as that given by Smith and Smith [illegible] for phenol red and diodrast. If, in the nomogram, P_f is referred to P without regard to W, the true stoichiometric relation would be distorted by variations in W and the nomogram would be applicable only to a particular sample of plasma with a certain value of W. By dividing P_f/P_w by W, one obtains a ratio P_f/P (as Smith and Smith reported it) that is independent of W. Generally one uses an average value of FW and avoids the determination of W.

† Sheehan [illegible] first used the terms 'extraction ratio' in connection with the removal of dyes from the blood perfusing the rabbit's kidney, but he did not study the concurrent excretion in the urine.

total volume of plasma perfusing the kidney (and all access tissue supplied by the renal artery and drained by the renal ve per unit time, i.e. the total renal plasma flow, RPF:*

(2)
$$\frac{C_x}{E_x} = RPF$$

As in the case of tubular reabsorption, tubular excretion in every instance that has been adequately examined is limited by a maximal rate of tubular transport. The rate of tubular excretion, T_x, is the difference between the total rate of excretion, U_xV, and the filtration rate of X, i.e.

(3)
$$T_x = U_xV - C_FP_xFW = \left(\frac{C_x}{C_F} - FW\right)P_x$$

As P_x increases, T_x increases proportionally until the tubular transport system becomes loaded to capacity, when T_x reaches its maximal value, Tm_x.

It was seen in chapter v that there are a number of independent transport systems involved in the tubular reabsorption of glucose, phosphate, sulphate, amino acids, etc. In tubular excretion, on the contrary, apparently all substances share a common element in one of two transport systems because, in all instances in which an adequate examination has been made, the loading of the tubules with one substance depresses the tubular excretion of all other substances in one of two groups. This is presumably a result of competition within the transport system rather than an inhibitory or toxic action, since it is freely reversible.

Tm_x is determined by maintaining P_x at such value that the load of X delivered to the renal tubules is substantially in excess of the actual quantity being excreted by the tubules, T_x; i.e. the load/T ratio should be 1.5 or greater. The load of X delivered to the tubules is calculated as the product of the volume of plasma perfusing the tubules times the plasma concentration, P_x. Actually, all the plasma which flows through the glomeruli perfuses the tubules, but any X contained in the glomerular filtrate is

* This statement takes no account of loss in the renal lymph or extraction from the red cells during passage through the renal circulation. The renal lymph flow is normally very small and loss by this route is apparently negligible, and most substances of practical importance do not enter the red cells in man.

thereby diverted into the lumen of the tubules and ceases to be part of the load available to them for excretion. One must therefore calculate this load as the total renal plasma flow, RPF, times P_x minus the quantity of X which is filtered, which is P_xC_FFW, or

(4) $$\text{tubular load of X} = P_x\text{RPF} - P_xC_FFW$$
$$= P_x(\text{RPF} - C_FFW)\ *$$

Since RPF cannot be measured simultaneously with Tm_x, it is conventional to substitute the clearance of X as determined just before elevation of P_x to high levels:

(5) $$\text{load}_x = P_x(C_x - C_FFW)$$

and the load/T_x ratio is

(6) $$\frac{P_x(C_x - C_FFW)}{T_x}$$

Alternatively, one may 'titrate' the kidneys with X in a manner wholly analogous to the titration with glucose (p. 87) and determine the load at which T_x becomes constant and maximal. Here one must assume that RPF remains constant during the titration process. So long as T_x increases in proportion to P_x, C_x will remain constant, but as soon as tubular saturation occurs and T_x no longer increases in proportion to P_x, E_x will begin to decrease (X will be carried into the renal vein in larger and larger quantities) and C_x will decrease. This depression of a clearance by overloading the tubules is called *self-depression* of the clearance, in contradistinction to the depression caused by some other competitive substance.

The evidence indicates that cellular 'storage' (involving a time factor as well as concentration) is not concerned in tubular ex-

* Another method of expression leading to the same result is to speak of the virtual volume of tubular perfusate as V_0, and to write:

(4a) $$V_0 = \text{RPF} - C_FFW$$

and

$$\text{tubular load} = P_xV_0$$

For the statistical analysis of tubular perfusion, this is a more convenient method of expression than the one above.

total volume of plasma perfusing the kidney (and all accessory tissue supplied by the renal artery and drained by the renal vein) per unit time, i.e. the total renal plasma flow, RPF:*

(2)
$$\frac{C_x}{E_x} = RPF$$

As in the case of tubular reabsorption, tubular excretion in every instance that has been adequately examined is limited by a maximal rate of tubular transport The rate of tubular excretion, T_x, is the difference between the total rate of excretion, U_xV, and the filtration rate of X, i.e.

(3)
$$T_x = U_xV - C_FP_xFW = \left(\frac{C_x}{C_F} - FW\right)P_x$$

As P_x increases, T_x increases proportionally until the tubular transport system becomes loaded to capacity, when T_x reaches its maximal value, Tm_x.

It was seen in chapter v that there are a number of independent transport systems involved in the tubular reabsorption of glucose, phosphate, sulphate, amino acids, etc. In tubular excretion, on the contrary, apparently all substances share a common element in one of two transport systems because, in all instances in which an adequate examination has been made, the loading of the tubules with one substance depresses the tubular excretion of all other substances in one of two groups. This is presumably a result of competition within the transport system rather than an inhibitory or toxic action, since it is freely reversible.

Tm_x is determined by maintaining P_x at such value that the load of X delivered to the renal tubules is substantially in excess of the actual quantity being excreted by the tubules, T_x; i.e. the load/T ratio should be 1.5 or greater. The load of X delivered to the tubules is calculated as the product of the volume of plasma perfusing the tubules times the plasma concentration, P_x. Actually, all the plasma which flows through the glomeruli perfuses the tubules, but any X contained in the glomerular filtrate is

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The variability of the results obscured the true relations of these clearances to the renal plasma flow.

In view of the importance, relative to the measurement of the renal plasma flow, of substances with high extraction ratios, such as phenol red, this group of compounds was subsequently re-examined in the writer's laboratory and the diodrast clearance at low plasma levels was developed into a renal blood flow method, while saturation of the tubules and the measurement of diodrast Tm at high plasma levels was utilized as a means of determining the quantity of functional (tubular) excretory tissue in the kidneys.* [1938]

Diodrast is marketed as a solution of the diethanolamine salt. The diodrast clearance is the same whether this salt or the diethylamine salt is administered,[188] which is to be expected since after dilution in the blood the nature of the original cation is a matter of indifference.

Titrations of normal subjects [1939] show that on the average the diodrast clearance is independent of plasma level up to about 5 to 6 mg/100 cc. of diodrast iodine, depending on the relative values of the renal plasma flow and Tm_D. On further elevation of the plasma level, a point is reached where tubular excretion (T_D) reaches a maximal rate (diodrast Tm or Tm_D), which remains unchanged at higher plasma levels. For the calculation of Tm_D, FW may be determined from the nomogram of Smith and Smith,[1950] taking into account the concentration of diodrast and of plasma albumin, or the average figure of 0.72, satisfactory for most practical purposes, may be used.[197]

How closely the diodrast clearance at low plasma levels approaches a complete clearance, or the total renal plasma flow, is obviously of importance. White,[2198] utilizing dogs with explanted kidneys to permit puncture of the renal vein, obtained an average extraction ratio, E_D, of 0.74 (range 0.61 to 0.88), while Corcoran, Smith, and Page,[425] by the same method, obtained 0.84 (range 0.79 to 0.96). Both groups of investigators agree that, although diodrast penetrates dog red cells very slowly *in vitro*, it penetrates rapidly *in vivo*, possibly during deformation of the cells in the capillary bed, and that about 25 per cent of this diodrast escapes from the cells during passage of the blood through the kidneys and hence becomes available for excretion, the actual clearance being thereby increased somewhat over the true plasma clearance. According

* Seeking some expression to convey the implication that functional measurements made under conditions of saturation represent the total quantity of tissue involved, the writer and his colleagues used the rather inept expressions 'tubular excretory mass' and 'tubular reabsorptive mass.' Happily, the expressions have never come into wide use and are abandoned without regret.

cretion, the substance involved being transported rapidly from plasma to urine without accumulation in the tubule cells. However, equilibrium between plasma and tubule cells is not instantaneous, and large errors can creep into clearance determinations if the plasma concentration is changing rapidly.

DIODRAST (DIODONE)

3,5-diiodo-4-pyridone-N-acetic acid

The quantitative study of renal plasma flow and of tubular function by saturation methods evolved historically in the sequence: phenol red, diodrast, and p-aminohippuric acid, the last named being now in almost universal use because of the ease with which it can be quantitatively determined Despite its historic precedence, the excretion of phenol red will be deferred until later in this chapter, but so much basic physiology has been worked out with diodrast that a rapid survey of its excretion is advantageous.

In recent years there have been introduced into urology various organic iodine compounds intended for intravenous administration or retrograde ureteral injection to aid in the x-ray visualization of the kidney, pelvis, or ureters. These compounds were developed commercially and selected from a number of candidate substances empirically. Most of them have proved on physiological examination to be excreted by the tubules, which of course enhances the concentration in the urine after intravenous administration. The three of greatest interest are diodrast, iopax, and hippuran, all of which have renal extraction ratios close to 1.0.

The fact that diodrast and hippuran are excreted by the tubules in the rabbit, dog, and man was first observed by Elsom, Bott, Shiels, and Walker[600, 601] and Landis, Elsom, Bott, and Shiels,[1206] who reported that the diodrast or hippuran/creatinine ratios in these species are considerably in excess of 1.0, and that the clearance ratios are depressed as the plasma concentration of the solute is increased. Elsom, Bott, and Walker[601] found that the ratio of the hippuran and phenol red clearances (as determined without due regard to dead space and other possible errors) in anesthetized rabbits sometimes exceeded by several fold the renal plasma flow as determined with a thermostromuhr, and they concluded that these substances had accumulated in the kidney in the interval between injection and the beginning of the clearance periods.

reported that the clearance of hippuran and phenol red in the rabbit might considerably exceed the renal blood flow as measured by a thermo-

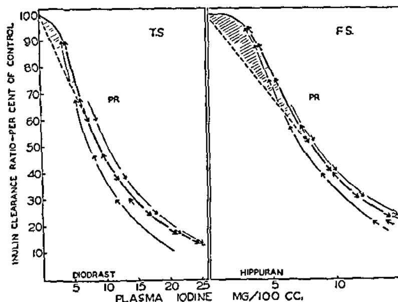


FIGURE 32. Observations in man designed to examine the possibility of storage of diodrast or hippuran in the renal tubules.

The light arrows indicate the effect of diodrast (left) and hippuran (right) on the phenol red/inulin clearance ratio when the plasma concentration of the iodine compound is rising, and again when it is falling rapidly. The heavy arrows indicate the clearance ratio corrected for a 150 second delay time The identity of the rising and falling curves when so corrected indicates that the tubule cells return to the initial equilibrium, as revealed by the urine they elaborate, very quickly after that initial equilibrium has been disturbed by exposure to high concentrations of diodrast or hippuran

The elevation of the phenol red/inulin clearance ratio above the expected level, as shown in the shaded areas, may be attributed to the accumulation of phenol red in the interstitial fluid of the kidney during the period of depressed excretion, or errors due to dead space and equilibration of blood and urine The total deviation, however, represents only a slight fraction of the total phenol red which passed through the kidney during the time when the phenol red clearance was depressed (Smith, Goldring, and Chasis [1938])

stromuhr, and they concluded that these substances were stored in the kidney. The point is of such fundamental importance, in the measurement of both renal blood flow and diodrast Tm, that Smith, Goldring, and Chasis [1938] re-examined the problem with diodrast and hippuran.

to White and Heinbecker,[2200] the total renal plasma flow in the dog would be calculated as 0.89 C_D/E_D, where E_D has a value of 0.74; according to Corcoran, Smith, and Page this calculation should be 0.943 C_D/E_p where $E_p = 0.84$; in both cases, the first factor takes account of the contribution of diodrast from the cells. By the first figure, total renal plasma flow * equals 1.2 C_D, by the second 1.12 C_D. Both groups of investigators used blood from the right and left renal vein indiscriminately, overlooking the fact that the extraction ratio (in both dog and man) in left renal venous blood will be lowered an indeterminate amount by the fact that the spermatic or ovarian vein empties into the renal vein on the left side of the body.[1893] Corcoran, Smith, and Page pointed out that the explanted kidney is subject to abnormal stresses, particularly on the renal vein, and frequently shows some thickening of the capsule, and hence the observed extraction ratio may not represent the normal average value in the kidney *in situ*. It seems probable that, when determination of E_D in the dog is made under conditions similar to those under which this value is measured in man, the average value corrected for diffusion from red cells will be about 0.90.†

The extraction ratio of diodrast in man is discussed on page 160. Some diodrast penetrates human and rabbit red cells *in vivo* [1183,1937,2196] (see table 11, p. 154), and White believes, on the basis of his observations in the dog, that some of this red cell diodrast is excreted in the urine. However, reasons are given elsewhere (p. 157) for believing that the extraction of diodrast from the red cells in man is negligible, and that the only correction involved is the overall plasma extraction ratio, which may be taken to be about 0.90. It is of interest that diodrast is secreted by the small intestine against a concentration gradient.

TUBULAR STORAGE

There appears to be no storage of diodrast (or of phenol red or hippuran) in the renal tubule cells. Goldring, Clarke, and Smith [800] showed that the phenol red clearance in man had the same value on a falling as on a rising plasma curve, but subsequently Elsom, Bott, and Walker [601]

* The extraction ratio obtained by White is perhaps lowered by the inclusion of observations in which the plasma diodrast concentration was as high as 13 mg per cent, under which conditions the clearance was probably self-depressed.

† E_D in the perfused isolated dog kidney is 0.62, this value rising when the perfusion pressure is lowered and the perfusion rate decreased. The ability of the tubules to excrete diodrast decreases progressively during the course of an experiment, however, and the initial figure is certainly below the value in the normal animal.[975]

tubular excretion in all nephrons. In this sense, Tm_D is also independent of glomerular activity, being a purely tubular function, but will increase or decrease if tubules are added to or removed from available circulation. Tm_D is fairly reproducible in any one subject, and is not modified significantly by adrenalin, caffeine, or renal hyperemia [1939]—a circumstance that indicates that all the tubules receive a uniform and fairly stable perfusion.*

Because it is a saturation phenomenon, Tm_D is susceptible to changes in body temperature; the temperature coefficient is not accurately known, but Goldring *et al*[787] believed this coefficient to be about 2.0, i.e. a rise of 1.0° F in body temperature increases Tm_D by about 10 per cent, and they recommended that the rectal temperature be recorded every 20 to 30 min. during Tm_D measurement and the observed value corrected to 98.5° F. by adding or subtracting 10 per cent for each degree above or below this value.†

Since tubular excretion in general appears to be a function of the proximal tubule, it is presumed that Tm_D is proportional to the total quantity of proximal excretory tissue. It is probably closely proportional to kidney weight in normal animals.

Goldring, Chasis, Ranges, and Smith [787] recommended the use of Tm_D to characterize the quantity of functional, tubular tissue in disease, and pointed out that measurements of renal plasma flow by the diodrast clearance (C_D) method could best be referred to the value of Tm_D in the same subjects, since the ratio C_D/Tm_D afforded an index of the renal plasma flow per unit of functioning tissue in any one individual. Normal values of C_D, Tm_D and C_D/Tm_D are given in table XII, page 544.

HIPPURIC ACID AND ITS DERIVATIVES

The analytical difficulties of determining organic iodine led the writer and his coworkers [1937] to search for other compounds having essentially complete clearances and amenable to easier analysis than diodrast. Hippuran has as high a clearance in man as diodrast (table II), and *a priori* it seemed that the presence of an atom of iodine in hippuran was not important in determining how the hippuric acid nucleus was handled by the renal tubules. The study of

* The use of the diodrast titration method to examine the dispersion of tubular perfusion per unit of excretory tissue is discussed in chapter XV.

† These investigators were unable to demonstrate a temperature effect on glucose Tm, and recommended that no comparable correction be made in this measurement until more information was available.[1938]

Instead of using the hippuran and diodrast clearances as the critical indicator of storage, they used the depression of the phenol red clearance, the reason for this choice being that the depression of the phenol red clearance is a much more sensitive indicator of the presence of hippuran or diodrast in the plasma, and presumably in the tubule cells, than are the self-clearances; a very small increment in the concentration of the iodine compounds, insufficient to produce appreciable depression of the self-clearance, produces a marked depression of the phenol red clearance and hence of the phenol red/inulin clearance ratio (fig. 32). The plasma concentrations of inulin and phenol red were kept constant by suitable intravenous infusions, while (a) hippuran or diodrast was introduced into the circulation in increasing concentration and raised to a high level; the administration of the iodine compound was then stopped and (b) the plasma level was allowed to fall, the rate of fall being extremely rapid since the clearances are large. When corrected for 'delay time' (transit time from an arm vein to urinary bladder, as discussed on page 60), as shown by the heavy arrows in figure 32, the phenol red clearances on the falling plasma iodine curve were identical with those on the rising curve, as indicated by the shaded area in figure 32, except at low plasma levels of iodine. This latter phenomenon may be attributed to the fact that, during the period when the tubular excretion of phenol red is depressed by diodrast and hippuran, the dye accumulates in the renal interstitial fluid in a concentration greater than that present when excretion is proceeding normally; on liberation of the excretory mechanism from depression by the iodine compound, this excess phenol red is available for excretion and, as calculated from the systemic plasma concentration, the phenol red clearance rises to slightly supernormal values. One may speak of this phenomenon as 'storage' of phenol red in the kidney as a whole, but not in the renal tubules, and it is negligible in magnitude even under the extreme conditions of these observations. Although the phenol red clearance was depressed to below 20 per cent of its normal value, the fraction of phenol red accumulating in the kidney was less than 2 per cent of the total quantity which would have been excreted had the clearance remained at its normal level. In no sense can the phenomenon be interpreted as indicating storage of diodrast or hippuran, which would depress rather than elevate the phenol red clearance.

DIODRAST Tm

Diodrast Tm (Tm_D) is in principle independent of the plasma concentration of diodrast and the rate of tubular perfusion, so long as their product, the tubular load, is adequate to maintain the maximal rate of

The discovery by Bunge and Schmiedeberg in 1876 that hippuric acid is synthesized by the kidney is a frequently cited landmark in biochemistry. These investigators showed that when sodium benzoate and glycine are injected simultaneously into dogs

curs if blood containing benzoic acid and glycine is perfused through the excised dog kidney and they concluded that, in the dog, benzoic acid is conjugated with glycine only in the kidney. This observation is especially noteworthy since it was the first molecular transformation of significance to general metabolism to be revealed in this organ Subsequent investigations have amply confirmed this discovery. Although the kidney is not the exclusive site of benzoic acid conjugation in man, it has been demonstrated by perfusion experiments to be capable of carrying out this operation.

When the higher homologues of benzoic acid are fed to mammals, they undergo various degrees of oxidation before conjugation This proceeds in general by β-oxidation, and Snapper and Grunbaum [1956] demonstrated that this oxidation can itself be carried out by the renal tissue. By perfusion of the kidney of the sheep, calf, and dog, they demonstrated that where phenylacetic acid is conjugated directly with glycine to yield phenylaceturic acid, phenylproprionic and phenylvalerianic yield hippuric acid, while phenylbutyric yields phenylaceturic acid. The dog's kidney, however, oxidizes phenylproprionic acid only to cinnamic acid, which is then conjugated to cinnamoylglycine, this organ being unable to oxidize cinnamic acid as do the kidneys of the sheep and calf.[1956 1957]

The maximal formation of hippuric, and probably of similarly conjugated acids, is dependent on the availability of glycine.

No data are available on the hippuric acid clearance, but that this compound is excreted by the tubules in the dog is demonstrated by the fact that the administration of sodium hippurate depresses the phenol red/creatinine clearance ratio.* [1937]

* The rate of excretion of hippuric acid in the Quick liver function test is independent of the urine volume [1778]

TABLE II

Comparison of Renal Clearances of Various Conjugated Aromatic Acids with the Diodrast Clearance

The clearance ratios in column 4 are calculated by the 3 different methods of comparison described in the text (from Smith *et al* 1937).

		Number of comparisons	X/diodrast clearance ratio	pK_a' 25° C.	*In vivo* cell/plasma distribution ratio per 100 gm water: Dog	Man
Clearances equal to diodrast:						
m-Hydroxyhippuric acid	dog	4	1.07	3.58		
p-Hydroxyhippuric acid	dog	4	0.98		0.3	
	man	6	1.04			0.16
	dog	3	0.98 *			
	man	3	0.97 *			
m-Aminohippuric acid	dog	4	1.00	4.18	0.41	
	man	3	0.99			0.0
p-Aminohippuric acid	dog	6	0.99	3.83	0.50	
	man	34	1.00			0.0
p-Acetylaminohippuric acid	dog	5	1.01	3.70		
	man	4	1.05			0.0
2-Pyridone-1-acetic acid	dog	2	1.06 †	2.94		
Cinnamoylglycine	dog	2	0.94 ‡	3.57		
Hippuran			1.00 §	3.63	0.65	0.49
Diodrast					0.73 ‖	0.38 ‖
Clearances less than diodrast:						
o-Hydroxyhippuric acid	dog	3	0.64	3.56		
	man	2	0.67			0.3
Iopax	dog	3	0.72	2.99	0.66	
p-Aminophenaceturic acid	dog	3	0.84			
Phenol red		8	0.56 ¶			
	man	8	0.58 **	7.9		

* With hippuran instead of diodrast as clearance of reference.
† With p-aminohippuric acid instead of diodrast as clearance of reference.
‡ The cinnamoylglycine clearance appears to be readily depressed by p aminohippuric acid.
§ Equated on basis of p-hydroxyhippuric acid ratios given above.
‖ White *et al* 1200 report 0.58 for the dog and 0.32 for man, while Corcoran *et al* 468 report 0.49 for the dog.
¶ Smith *et al* 1938.
** Phenol red/hippuran clearance ratio (Smith *et al* 1938).

various hippuric acid derivatives disclosed that they had the same clearance values as hippuran and diodrast in both dog and man, and from them p-aminohippuric acid was selected for practical use.[362]

at least so far as urine collection and timing errors are concerned, by comparing the inulin or creatinine clearance ratios, since such errors cancel out in the calculation of a clearance ratio.

3. The simultaneous clearances obtained in the second half of the experiment may be compared directly.

Table 11 summarizes the average clearance ratios as determined by successive and simultaneous clearances in the dog and man. m-hydroxy-, p-hydroxy-, m-amino-, and p-aminohippuric acids, hippuran (o-iodohippuric acid), 2-pyridone-1-acetic acid (the nucleus of diodrast), and cinnamoylglycine all have clearances identical, within the experimental error, with that of diodrast, in both dog and man. The identity of the p-aminohippuric acid and diodrast clearances is maintained in a variety of diseased states, including hypertensive disease and chronic glomerulonephritis, where the clearance of all compounds is substantially reduced. The clearances of o-hydroxyhippuric acid, iopax, p-aminophenaceturic acid, and phenol red are distinctly lower than diodrast but nevertheless of a high order of magnitude. There is no simple relation between tubular excretion and chemical structure, as shown by o- and m-hydroxyhippuric acids, nor is pK_a' important, as shown by the fact that the clearance of phenol red (7.9) compares favorably with that of iopax (2.99).

In discussing the excretion of diodrast, it was noted that this compound penetrates both human and dog red cells *in vivo*, although not *in vitro*, the hippuric acids also penetrate the red cells of the dog *in vivo*, and o- and p-hydroxyhippuric acid and hippuran penetrate human red cells, but m- and p-aminohippuric acids do not. White's [2201] supposition that a significant quantity of this intracellular diodrast is extracted and excreted during the passage of the blood through the kidneys is, the writer believes, controverted by the identity of the [illegible]

simultaneous clearances of this compound and of diodrast remained identical throughout, despite marked changes in renal plasma flow. It is therefore believed that cell transport does not contribute to the diodrast clearance in man, and that, in the cal-

HIPPURAN

The first studies [1938] of the excretion of hippuran and diodrast at constant plasma levels in 4 subjects showed (in non-simultaneous observations, which were impractical because both involved the determination of organic iodine) that the inulin/hippuran clearance ratio averaged 0.185 and the inulin/diodrast clearance ratio, 0.166. The difference between these figures is probably not significant, and this apparent identity, coupled with the qualitative demonstration of the tubular excretion of hippuric acid itself, led to the investigation by Smith, Finkelstein, Aliminosa, Crawford and Graber [1937] of the excretion of various hippuric acid derivatives and related compounds, as listed in table 11.*

The examination of the relative clearance values of two compounds both of which are excreted by the tubules presents difficulties. When two such substances are presented to the tubules simultaneously, one may depress the tubular excretion of the other, and the conventional method of comparing simultaneous clearances may thus lead to erroneous results. Consequently both the 'successive' and 'simultaneous' methods of comparison were used, the compound with the strongest competitive power (diodrast) being administered last. There were thus afforded 3 methods of comparison:

1. Comparison of successive clearances, wherein the clearance of the hippuric acid derivative (or other compound) was measured alone in 3 consecutive periods, followed by a similar 3-period determination of the diodrast clearance simultaneously with the clearance of the first compound

2. In method (1) changes in the renal plasma flow or errors in collection and timing of urine may jeopardize the comparison of the absolute clearance values so obtained. This hazard is obviated,

* Hippuran Tm has been determined in only 3 subjects, and averaged 76 mg iodine per 1 73 sq. m/min In 1 subject phenol red Tm was 0.10, diodrast Tm 0.32, and hippuran Tm 0.63 mM/min.

The fact that diodrast Tm in mM is twice as great as hippuran Tm does not require that the extraction ratio of hippuran be less than that of diodrast, both compounds will have a maximal extraction ratio (c 1.0) at low plasma levels

Hippuran depresses the phenol red clearance and, mM. for mM., this action appears to be identical with that of diodrast. Iopax appears to be equally effective in this respect, but neoiopax is definitely less effective.

conjugation would not be important in the use of PAH in determining the renal plasma flow unless this conjugation occurred in transit across the renal tubule cells (which apparently is not the case [*vide infra*]), since only unconjugated PAH is determined in the plasma and urine.

Beyer, Mattis, Patch, and Russo [140] have shown that trypsin and carboxypolypeptidases do not hydrolyze PAH *in vitro*, and probably not *in vivo*. The nephrectomized rat conjugates the p-amino group, but more slowly than it conjugates sulfathiazol, etc. PAH does not antagonize the bacteriostatic activity of sulfanilamides It is only slowly absorbed from the gastrointestinal tract, whereas p-aminobenzoic acid is fairly rapidly absorbed.[1302] Mattis, Beyer, McKinney, and Patch [1418] have shown that PAH is relatively non-toxic, convulsive symptoms in dogs appearing only when the plasma concentration exceeds 400 mg. per cent.

The rapid intravenous injection of strong PAH solutions for priming prior to the determination of Tm_{PAH} may lead to vasomotor disturbances, flushing, tingling, cramps, nausea, and rectal contraction These disturbances can be diminished or avoided by slowing the infusion momentarily. It is believed that they are in part referable to the sodium ion, since strong salt solutions may have the same effect *

* Raaschou [1565] reports that Brun, Hilden, and himself, after the infusion of inulin and diodrast into normal persons having a very heavy water load to promote diuresis, repeatedly saw indisposition, nausea, vomiting, sensation of cold, oliguria, pallor, slight cyanosis, fainting, and pyrexia, but that such symptoms were never observed among a series of patients who drank only

decreasing from 0 181 to 0 144.

This vasomotor complication during the measurement of Tm_{PAH} is perhaps not solely referable to PAH itself During the early period of use of this compound, when all available material was synthesized in glassware and yielded an almost colorless 20 per cent solution, such reactions were less severe Analysis of a number of observations made by the writer's colleagues reveals that before April 1946, in the vast majority of instances, the filtration rate *increased* after the priming dose for Tm, the modal increase being 10 to 15 per cent After that date, the filtration rate in the majority of instances has decreased At an in-

culation of the total renal plasma flow, only the plasma extraction ratio should be taken into account.

Other conjugated aromatic acids are excreted by the tubules and have complete or nearly complete clearances: p-aminophenaceturic acid and cinnamoylglycine, as shown in table 11, and various penicillins and cinchoninic acid derivatives (*vide infra*). This fact suggests that tubular excretion may represent a teleological adaptation promoting the excretion of difficultly metabolizable aromatic acid residues after conjugation, though this simple statement does not explain the tubular excretion of phenol red and other sulfonephthaleins.

CLINICAL USE OF p-AMINOHIPPURIC ACID (PAH)

In view of the facts that at low plasma levels the PAH clearance is identical with that of diodrast and hence equally valid as an estimate of the renal plasma flow, that the chemical determination is simple, that the endogenous plasma and urine blanks are negligibly small, that it does not penetrate the human red cell *in vivo*, that it is non-toxic and can be used for the evaluation of total tubular excretory tissue, and that it is less extensively bound by plasma proteins than is diodrast and hence errors involved in the estimation of the filtrable fraction in the plasma are of less practical consequence, p-aminohippuric acid has been recommended as a substitute for diodrast in laboratory and clinical investigation.*[262, 795]

The free amino group in PAH is conjugated (presumably with acetic acid to form acetyl PAH) in man,[1937] rabbit (unpubl. obs.), and rat,[140] but not in the dog,[1937] these interspecies differences being entirely parallel with those observed in the conjugation of the p-amino group in sulfanilamide, etc. (*vide infra*). p-Acetylaminohippuric acid also has a maximal clearance, but in any case

* PAH as a 20 per cent sterile solution of the sodium salt is available from Sharp and Dohme, Glenolden, Pennsylvania. Analytical methods and clearance determinations in the dog are described by Smith *et al.*,[1937] and clearance determinations in man are described by Goldring and Chasis[795] and Chasis, Redish, Goldring, Ranges, and Smith.[262]

In the determination of mannitol by the periodate oxidation method, the p-amino group of PAH is oxidized and leads to significant errors.[66] Similarly PAH interferes with the determination of thiosulphate.[795]

TABLE III

Renal Extraction Ratios of Diodrast and PAH in Dog and Man

Species	Number of determinations	Method *	Kidney	Substance	Mean	E (plasma) range	
Dog		EK	Both	D	0.74	0.61 –0.85	White [2193]
Dog		EK	Both	D	0.84	0.79 –0.96	Corcoran *et al.*[428]
Dog	9	EK	Left	PAH	0.87 ± 0.04		Phillips *et al.*[1606]
Man	8	VC	Both	PAH	0.904	0.85 –1.00	Warren *et al*[2144]
Man	22	VC	Right	PAH	0.925	0.875–1.00	Bradley *et al.*[230, 234, 239, 240]
Man	6	VC	?	PAH	0.926	0.860–0.954	Reubi *et al*[1699]
Man	4	VC	Right	PAH	0.900	0.890–0.910	Sirota[1903]
Man	29	VC	Right	PAH	0.922	0.810–0.960 †	Breed *et al.*[250]
Man	10	VC	Right	PAH	0.900	0.830–0.930	Cargill[328]
Man	8	VC	Right	PAH	0.90	0.88 –0.91	Mokoloff (pers. com.)
Man	3	VC	Right	PAH	0.94	0.90 –0.98	Werkö *et al.*[2170]
		Weighted average for PAH in man			0.912		

* EK, explanted kidney, VC, venous catheterization

† Only one below 0.880

EXTRACTION RATIOS OF PAH AND DIODRAST

The development of venous catheterization for the collection of venous blood from the right heart, initiated by Cournand and Ranges[438] for the determination of the cardiac output by the direct Fick method, is easily extended to the collection of pure venous blood from the renal vein. When properly applied, it affords a reliable method for determining the renal extraction ratio of any substance under conditions avoiding all disturbance of the renal circulation. The method suffers the limitation that renal venous blood should not be drawn on the *left* side of the body in either dog or man, because in some individuals significant quantities of non-renal blood may enter the renal vein close to the hilus via the spermatic or ovarian veins, as Marshall[1393] long ago recognized in utilizing one of these veins to obtain renal venous blood without puncturing the renal vein. The presence of non-renal venous communications into the renal vein on the right side of the body, though relatively rare, cannot be invariably excluded and may account for an occasional low extraction ratio obtained in some subjects. The precaution must be taken not to contaminate the renal venous blood with blood from the inferior vena cava; this difficulty can be avoided by allowing the syringe to fill as much as possible by venous pressure, and gross error from this source can be detected by the presence of a high arterial-venous oxygen difference, this figure for inferior vena caval blood being generally 4 cc/100 cc. or more, whereas the figure for renal blood generally lies between 1 and 2 cc/100 cc. Novocaine or procaine must not be used since these compounds react in the PAH method and increase the venous blank significantly. It is the practice in the writer's laboratory to determine all blanks in both arterial and venous blood, since at times they seem to differ significantly.

The data presented in table 11 on the relative magnitudes of the diodrast and PAH clearances in dog and man leave no doubt that these are identical, and identical with m-hydroxyhippuric, p-

determinable date prior to April 1946, the manufacture of PAH was begun on a commercial scale, using porcelain or metal reactors, and since then the 20

92 per cent. That any compound should be so completely removed from the blood during its transit through the kidney is a matter of some surprise. It cannot be supposed that all the blood entering the renal artery is distributed to tubular excretory tissue, since some of it must pass to the renal vein by way of perirenal fat and inert tissue in the renal capsule, pelves, and calyces; however, this uncleared blood can represent no more than 8 per cent, in the mean, of the total renal blood flow. It seems probable that the extraction of diodrast or PAH in the blood which actually perfuses the excretory tissue is very close to 100 per cent complete.

The PAH clearance divided by E_{PAH} gives the *total* renal plasma flow, i.e. *absolutely* all the plasma moving between the renal artery and the renal vein.* It is generally not possible to determine E_{PAH} in clinical observations, and the majority of available data record only the uncorrected clearance, C_{PAH}. It must be recognized that this value is not identical with the total renal plasma flow; it represents the volume of plasma presented for clearance to the functioning renal parenchyma, a volume which we may take as 92 per cent, on the average, of the total renal plasma flow. Because of this qualification, it is desirable to designate the PAH clearance as the 'effective renal plasma flow,' as was pointed out for the diodrast clearance by Smith, Goldring, and Chasis.[1938] The expression is, however, cumbersome on repetition, and most investigators have simply spoken of the diodrast or PAH clearance as the 'renal plasma flow,' a usage which is so well established that it is not readily abandoned. It would seem appropriate to continue this identification, and to designate the 'total renal plasma flow' (C_{PAH}/E_{PAH}) by these terms, or some suitable expression showing that E_{PAH} has actually been determined simultaneously with C_{PAH} and used in the calculation of the designated figure. The

* Wolf[illegible] has pointed out that, for substances with a low extraction ratio, the abstraction of the urinary water from the blood must be allowed for in calculating the renal blood flow. The proper equation would be

$$RPF = \frac{V(U - R)}{(A - R)}$$

where U, R, and A are concentrations in the urine, renal venous, and arterial plasma. For substances with as low an extraction ratio as urea or inulin, neglect of the V term may lead to errors in RPF of 4 to 14 per cent, but the correction may be omitted with PAH.

hydroxyhippuric, m-aminohippuric, p-acetylaminohippuric, pyridone-1-acetic acids, cinnamoylglycine, and hippuran. In tw long experiments in man, involving pyrogenic hyperemia, th PAH and diodrast clearances remained identical throughout, de spite a marked increase in both clearances. Newman *et al.*[1515] have recently confirmed the identity of the PAH and p-acetylamino-hippuric acid clearances in man. From this identity, it may confidently be concluded that in the normal kidney the upper limit in clearance value is the available renal plasma flow rather than any limitation in the tubular excretory mechanism. Table III presents extraction ratios reported for diodrast and PAH by various investigators. The extraction ratios of diodrast reported in the explanted kidney of the dog are significantly below those observed in man using the venous catheterization technique. Presumably this does not represent a true species difference but reflects the development of collateral circulation through inactive tissue between the renal artery and vein in the dog, or escape of material from the red cell into the plasma after the blood has left the kidney. However, a definite answer will not be available until extraction ratios have been determined in the dog by the catheterization method.*

MEASUREMENT OF THE EFFECTIVE RENAL PLASMA FLOW, THE TOTAL RENAL PLASMA FLOW AND Tm_{PAH}

On the basis of the data in table III, we may take the average normal extraction ratio of diodrast (E_D) or PAH (E_{PAH}) in man as

* As noted above, Smith *et al*[1397] confirm that diodrast penetrated the red cells *in vivo* in both dog and man, but PAH penetrates the cells only in dog, *not in man;* the last point has been confirmed by Barker *et al.*[11] Phillips *et al.*[1606] showed that before centrifugation of dog blood at room temperature can be completed a significant quantity of PAH diffuses from the cells into the plasma, decreasing E_{PAH} by an average of about 5 per cent. When left renal venous blood was chilled and centrifuged immediately, E_{PAH} averaged 0.87 with a aximal variation of ±9 per cent. The figure would possibly have been higher ad the right kidney been used. Despite the fairly rapid diffusion of PAH out the cells *in vitro*, Phillips *et al* conclude that there is no diffusion from cells plasma as the blood traverses the postglomerular circulation, because the served changes in cell content between arterial and venous blood can be ounted for by diffusion in drawn blood and the time of exposure of blood he postglomerular circulation is less than one-fortieth of a minute, assuming the kidney contains 10 per cent blood and the blood flow is 4 cc/min. per gm.

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terms 'total renal plasma flow' will be used in this volume for such corrected values. Unless extraction ratios are measured concurrently with clearances, it seems undesirable to apply any correction to the clearance (effective plasma flow); this datum has physiological value in its own right (particularly in the ratio C_{PAH}/Tm_{PAH}), and the publication of corrected and uncorrected data without clear differentiation would only lead to confusion. If correction for E_{PAH} is made, it should be so stated and the plasma flow so obtained perhaps designated the total renal plasma flow.

CALCULATION OF WHOLE BLOOD FLOW

Where it is desirable to record the data in terms of whole blood, the appropriate values can be calculated either as

$$\text{Effective renal blood flow} = C_{PAH}/(1 - \text{hematocrit})$$

or

$$\text{True renal blood flow} = C_{PAH}/E_{PAH}(1 - \text{hematocrit})$$

In this calculation it should be recognized that the volume of plasma trapped between the red cells in a well centrifuged hematocrit amounts to about 5 per cent of the red cell volume;[858, 1606, 2096] for very precise purposes (estimation of renal fraction, etc.) it may prove to be desirable to make this correction by deducting 5 per cent of the volume of the red cells in reading the hematocrit. This correction has, however, rarely been made and for general purposes may be neglected.

Tm_{PAH}

The tubular excretion of p-aminohippuric acid is limited by a constant and reproducible maximal rate (Tm_{PAH}) in both dog[1857] and man.[382] Tm_{PAH} may be used, like Tm_D, to characterize the quantity of tubular excretory tissue in health and disease. A titration of a normal subject with PAH is shown in figure 33.

Tubular function is clearly under the trophic influence of the anterior pituitary gland (ch. XV) and subject to changes in tubular metabolism. Mudge and Taggart[1490] have shown that in the dog the infusion of acetate (0.06 to 0.21 mEq/min. per kg.) or lactate (0.11 to 0.13 mEq/min. per kg.) increases Tm_{PAH}, in the first in-

stance, by 44 to 85 per cent. There is a concomitant increase in the filtration rate, but the increase in Tm_{PAH} is clearly related to increased availability of acetate and lactate for tubular metabolism. Fumarate and succinate inhibit tubular excretion of PAH. The acceleratory effect of acetate is so striking that Cross and Taggart [455] suggest that it may constitute the rate limiting cellular constituent in PAH transport. It is clear that under conditions which may affect acetate or lactate metabolism Tm_{PAH} cannot be expected to remain constant.*

Eggleton and Habib [584] have shown that PAH is excreted in the cat in the same manner as in the dog and man: at a low plasma concentration the clearance is independent of change in concentration and may be used as a measure of minimal renal plasma flow. As the plasma concentration is increased, T rises to a maximal (Tm) of 20 to 30 mg/min per 100 cc. of filtrate, Tm being reached at about 10 mg/100 cc. of plasma. FW appears to have a value of 0.91.† At concentrations greater than 30 mg/100 cc., Tm_{PAH} apparently decreases and at high concentrations the total amount excreted approaches the filtered load. The authors attribute this decreased excretion to passive reabsorption. Tm_{PAH} is also depressed by a high concentration of creatinine These observations were made with rapidly changing plasma concentra-

* Cross and Taggart [455] have shown that acetate to a notable extent, and to a lesser extent lactate and pyruvate, accelerate the accumulation of PAH and PAAH in slices of rabbit's kidney incubated *in vitro* Minimal effects were produced by glucose, hexose diphosphate, proprionate, butyrate, acetylglycine, isobutyrate, acetoacetate, and oxalacetate Ethanol, acetaldehyde, and diacetyl were completely inactive, while α-ketoglutarate, succinate, fumarate and malate, glycine, alanine, and glutamate all exerted an inhibitory effect Various enzymes were without effect PAH accumulation is inhibited by 2,4-dinitrophenol and certain related compounds which inhibit aerobic phosphorylation.

2,4-Dinitrophenol inhibits the tubular excretion of PAH, diodrast, and phenol red in the dog, with no significant changes in renal hemodynamics,[1489] and with no effect on Tm_G

Tm_D is also increased by testosterone, thyroxin, and thyroid extract (ch xv) and vitamin A, and Tm_{PAH} by vitamin A (ch xv) The results with lactate

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2,4-Dinitrophenol inhibits the tubular excretion of PAH, diodrast, and phenol red in the dog, with no significant changes in renal hemodynamics,[1059] and with no effect on Tm$_G$

Tm$_D$ is also increased by testosterone, thyroxin, and thyroid extract (ch xv) and vitamin A, and Tm$_{PAH}$ by vitamin A (ch xv) The results with lactate may bear on the increase in Tm$_{PAH}$ in dogs during altitude anoxia (ch. xiv)

† These authors incorrectly quote Smith *et al* [1081] as failing to obtain evidence that PAH is not freely filtrable through a collodion membrane What Smith *et al* found was that PAH was destroyed (by oxidation of the amino group by the nitro groups of the collodion) in such membranes, and that reliable ultrafiltration experiments could therefore not be obtained.

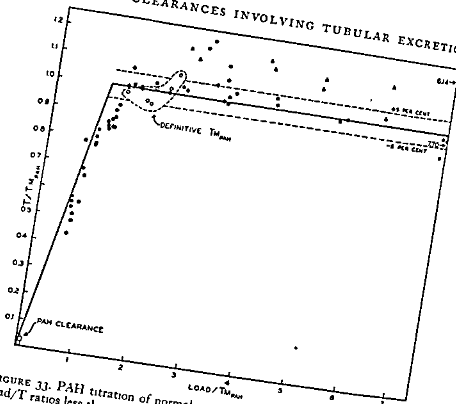


FIGURE 33. PAH titration of normal 53-year-old male The PAH clearance at load/T ratios less than 0 1 on 3 occasions was 670, 565, and 635 cc. The average figure of 623 cc was used to calculate V_0. Definitive TM_{PAH} was determined from 7 observations (circles) at a load/T ratio of 1.3 to 2 2. Titrations with constant plasma concentrations at each point were determined on 7 different occasions at load/T ratios as high as 8.14 The triangles represent determinations made on the fourth occasion, and are all higher than other observations by about 15 per cent. An abrupt change in Tm_{PAH} of this magnitude is unusual, but may be anticipated in view of the evidence on endocrine influence on tubular function (ch. xv)

It will be noted that there is no evidence of depression of tubular excretion of PAH at these high loads

The splay in the titration curve at load/T ratios from 0.5 to 1 3 may in part be attributable to the reduction in total renal plasma flow associated with the known vasomotor disturbances and reduction in filtration rate induced by large doses of PAH. The average deviation from the rectilinear relationship is, however, less than 10 per cent.

The maximal plasma concentration of PAH reached was 167 mg/100 cc. At no time were there adverse subjective or objective reactions (Maxwell, Morales, Crowder and Fishman, pers. com)

tions and no information is available on the time effect of a constant plasma concentration. A similar depression of Tm_D at high plasma concentrations of diodrast has been reported by Barclay, Cooke, and Muralt.[81] Eggleton and Habib suggest that this phenomenon may be attributable either to a combination of tubular excretion and passive diffusion, the latter process varying with the concentration gradient from tubular urine to plasma, or to a toxic action on the tubule cells. It seems plausible, however, in view of the studies of Taggart and his coworkers, cited above, and the rapid reversibility of Tm with rise to supernormal values on recovery at reduced plasma concentrations, that the self-depression of Tm_{PAH} and Tm_D at high plasma concentrations may be related to exhaustion of some component in the metabolic system involved in tubular transport. This explanation would not account for the fact that excretion during the depressed state may apparently be less than the filtered load, but these negative values are small and can be accepted only after examination at constant plasma levels in order to rule out all the sources of error discussed in chapter III. This self-depression of Tm_{PAH} may be observed in the dog when the load/Tm ratio exceeds 4 or 5, but it is inconstant and may be absent at ratios above 10 (Schachter and Freinkel, pers. com.). In the single critical study available it was not observed in man at load/Tm ratios as high as 8.0 (fig. 33), far above those required for the clinical determination of Tm.* Until further information is available, Tm_{PAH} and Tm_D should obviously be measured at moderate load/T ratios with constant plasma concentrations and substantiated by observation of three or more consecutive periods.

* In the calculations shown in figure 33 FW was taken as 0.83, as estimated by Chasis and his coworkers[illegible] from data on $\Delta UV/\Delta P$ in man on falling plasma concentrations. In retrospect it must be admitted that this method is open to substantial errors. Taggart (pers. com.), using dialysis through Visking (cellophane) tubing, seemingly a very reliable method, finds that in human plasma with 5 per cent albumin and at PAH concentrations from 30 to 50 mg/100 cc., FW = 0.78 to 0.79 (W = 0.90). In the dog, FW is grossly independent of P up to 60 mg/100 cc. and averages 0.917. Eggleton and Habib,[illegible] using the clearance method, report 0.91 in the cat. Tm_{PAH} data in man calculated with FW = 0.83 are reported in this volume.

Data on the filtration rate, renal plasma flow, renal blood flow, Tm_D and Tm_{PAH} in man and dog are summarized in chapter XXII.

SINGLE INJECTION METHOD

The errors involved in the use of single injection methods have been discussed earlier (p. 57). They are particularly large with any substance cleared as rapidly as PAH. The writer and his colleagues prefer to continue with the use of steady concentrations of both inulin and PAH, maintained by constant intravenous infusion, established after the administration of a suitable priming dose.* Newman and his co-workers [1515] have recently recommended that the priming injection be omitted, since they believe that a constant plasma level can be established some 20 min. after a constant infusion has been started. However, Barker, Clark, Crosley, and Cummins [88] find that 75 min. are required to reach 90 per cent of the eventual level, since the volume of distribution of PAH in man is greater than Newman *et al.* estimated.†

ERRORS DUE TO RENAL CONJUGATION OF PAH AND TO LYMPHATIC DRAINAGE

A further source of error, possibly referable to the kinetics of tubular excretion, has been reported by Newman, Kattus, Genecin, Genest Calkins, and Murphy.[1515] In man, when the plasma level of diodrast is falling, whether after a single injection or following a sustained higher level, the clearance is markedly depressed. A similar phenomenon occurs with PAH in man,[1024] but not in the dog. The clearance of p-acetylaminohippuric acid in man, however, is unaffected by decreasing plasma concentration, and the authors suggest that the transient depression of the PAH clearance on a falling curve may be related to conjugation in the kidney.

Hamburger and Ryckewaert [893] report that the PAH clearance in man is very low when determined at plasma levels under 1.0 mg/100 cc., some of their observations being made after a single injection and some

* The priming dose may be calculated on the basis that the volume of distribution of inulin in man averages 16 per cent of the body weight, that of PAH 28 per cent. The rate of infusion, IV, should then be adjusted so that IV will equal UV with the expected rate of clearance.

† The authors find the volume of distribution of PAH to be 35.9 ± 7.3 per cent of the body weight, but their method involves calculation by differences. By the overall clearance-slope method, Schwartz [1604] finds 28.5 and 26.2 per cent of the body weight in 2 men and 27.5 and 26.6 per cent in 2 dogs, while Houck [1039] obtained an average volume of distribution in 16 nephrectomized dogs of 28 per cent of the body weight

during infusion They suggest that the low clearance may be due to tubular conjugation, high plasma protein binding, or tubular inertia. In view of the results obtained by Newman *et al*, the last two explanations may be ruled out The possibility of extensive total conjugation in the kidney when tubular transport is small cannot certainly be excluded, but in the absence of evidence that diodrast is conjugated or metabolized, this supposition does not explain the depression of the diodrast clearance on a falling curve Moreover, the fact that the PAH and diodrast clearances in dog and man are identical at plasma PAH concentrations of 0 7 to 2 5 mg/100 cc. and diodrast concentrations of 0.5 to 2.5 mg iodine per 100 cc,[197] * where E_{PAH} is 0.92, argues against any significant renal conjugation or metabolism of either substance at low plasma levels Whatever the explanation, it is clear that recorded clearances in man obtained on falling diodrast and PAH curves are possibly all erroneously low Baldwin, Villarreal, and Sirota (pers com) have compared 24 clearances of free and total (free + conjugated) PAH in 9 subjects, and find that the total PAH clearance exceeds the free PAH clearance by an average of 4 per cent. They find, however, that there is a slight loss of p-acetylaminohippuric acid † during hydrolysis in plasma filtrates, without a corresponding loss in urine, and they believe that this loss accounts for the differences in clearances.

Conjugation other than in the kidneys has no effect on the accuracy of the PAH clearance as a measure of the renal plasma flow, since only free PAH is determined in plasma and urine.

RENAL LYMPH

Unfortunately, very little is known about the formation of lymph in the kidneys Schmidt and Hayman[1786] demonstrated in the dog that there is a small but significant flow of fluid, ranging from 0 04 to 0 60 cc/min. Sugarman, Friedman, Barrett, and Addis[2022] cannulated the capsular and hilar lymphatic trunks and demonstrated by the injection of dyes into the renal artery, the cortex, and the medulla that the lymphatic flow from the cortex is into the capsular lymphatics and from the medulla into the hilar lymphatics The protein content of renal lymph varied from 0 4 to 4.0 gm/100 cc. The slower the flow, the greater in general was the protein concentration The urea concentration was always greater, often considerably greater, than in the arterial or renal

* The writer has checked the plasma concentrations of PAH and diodrast in the clearance comparisons reported in table 11, and finds that they fall within these ranges

† This compound is not deacetylated in man, according to Newman *et al*[illegible]

venous plasma. Kaplan, Friedman, and Kruger[1099] have shown that the glucose content of renal lymph is practically as high as that of cervical lymph or plasma. During the infusion of inulin, the concentration of this substance in renal lymph remains substantially below that of cervical lymph, in which the concentration is only slightly less than that in plasma. The authors conclude that renal lymph is derived from both plasma (peritubular capillaries, etc.) and tubular reabsorbate. The presence of urea in concentrations exceeding that of plasma reflects the back diffusion of urea from tubules to capillaries. In the thin limb, distal tubule, and collecting ducts the concentration gradient may be very steep. Kaiserling and Soostmeyer[1087] report that in rabbits, after ligation of the renal lymphatics leaving the hilus of the left kidney, the volume of the kidney almost doubled in 15 min., and this kidney thereafter excreted a larger volume of more dilute urine than the kidney on the unoperated side, while the first appearance time of indigo carmine was prolonged by 90 sec. on the operated side.

The renal interstitial fluid presumably contains inulin at a concentration not far below that in the plasma circulating in the peritubular capillaries, whereas the concentration of PAH would be much lower because of continued removal by the tubules. If the lymphatic drainage were significant, more inulin than PAH would be carried away in the lymphatics, and the inulin clearance would decrease more than would the PAH clearance. A discrepancy from this source would be revealed by calculating the total renal plasma flow from C_{IN}/E_{IN} and C_{PAH}/E_{PAH}. Cargill[228] has made such calculations in man, and finds that in general the two methods agree well, the average in 28 patients being 497 for the first datum and 466 for the second. The fact that C_{PAH}/E_{PAH} is lower than C_{IN}/E_{IN} argues against significant lymphatic loss, though it is in line with the supposition that a small quantity of PAH may be conjugated in the kidney. In the data of Corcoran and Page,[411] C_{IN}/E_{IN} and C_{PR}/E_{PR} agree remarkably well. In such calculations it must be remembered that the calculation of E_{IN} by the arterial-venous inulin difference involves large errors, and before significant loss in the renal lymph can be argued great accuracy must be demonstrated for these analyses.

PAB AS A CONTAMINANT IN PAH

p-Aminobenzoic acid (PAB) has a low clearance[1937] and, if present as a contaminant in PAH, would tend to lower the apparent PAH clearance. The isolation of PAB from a single commercial sample of PAH has been

recorded by Schreiner, Wesson, and Anslow.[1102] The commercial material is now safely guarded against this accident.

PAB CLEARANCES

PAB is rapidly absorbed from the gastrointestinal tract in dog and man, whereas PAH is poorly absorbed. When taken orally, PAB is conjugated in man to form derivatives, in part no doubt PAH, which have as a mixture a relatively high clearance, but apparently somewhat below PAH except at plasma levels below 1.5 mg/100 cc. (Wesson, pers. com.)

PHENOL RED

The excretion of phenol red (phenolsulphonephthalein) is of particular interest because of the important role it has played in the history of renal physiology.

Phenol red was introduced by Rowntree and Geraghty in 1910 as a renal function test after these investigators had found that, among a large number of dyes tested in normal animals, this was excreted most rapidly by the kidneys. It was further shown that the rate of its excretion was greatly reduced in man in advanced glomerulonephritis. Rowntree and Geraghty's phthalein or PSP test, which consists of injecting a small, accurately known quantity of dye intramuscularly or intravenously and noting the fraction recovered in the urine in successive periods thereafter, has been widely used to test renal function in man. The value of this test rests upon empirical correlation with other clinical data and does not involve any consideration of how the dye is excreted.

The question whether phenol red is excreted exclusively by filtration or in part by tubular excretion was long a subject of controversy. Like many other substances, it enters into combination with plasma albumin,[804] the combination is reversible, the equilibrium between free and bound dye depending upon the concentration ... The binding of ph... anc ... the ... dye ... ... passed through the glomeruli, ... postulate that the protein-... reabsorbed by the tubules. Marshall and Vickers[1107] ... planation in favor of the belief ... the proteins being the ... ejected this ex-... onst ... he dye from the ... They dem-... ... ules in the cortex of the ... jection of phenol red into the dog, when the blood pressure is too low to permit the formation of significant

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respectively, 0.94, 0.83, 0.58, 0.67, and 0.85. The values of Km are 3.55, 2.32, 17.20, 2.8, and 0.62. K has been determined only in man, in whom it has the value of 0.85, a value which appears to be unaffected by disease. Since the constant 1/n is less than 1.0 in all 4 species, *the fraction of unbound dye in a given sample of plasma increases as the total concentration of dye is increased*. The equilibrium between bound and total dye in human plasma having different albumin contents has been expressed in a nomogram by Smith and Smith.[1950]

Richards and Walker[1717] found that the concentration of dye in the capsular fluid of the frog approximates the concentration of unbound dye in the plasma, as would be demanded by theory and the collateral evidence on the nature of glomerular filtration.

As noted in the early part of this chapter, the tubule cells, by taking up the unbound dye that has escaped from the capillaries, reduce the concentration in the peritubular fluid; this reduction in concentration promotes diffusion of unbound dye from the capillaries and, with the reduction of the concentration of unbound dye in the capillaries, the bound dye dissociates, so that in theory all the dye, both bound and unbound, is available for excretion. When we note the great expanse of peritubular capillaries, it is not surprising that tubular activity can remove a large fraction of the dye from the blood flowing through the kidney before this blood emerges into the renal veins. The primary limiting factor is probably the speed of diffusion of unbound dye through the peritubular fluid separating the capillaries from the tubule cells.

TUBULAR EXCRETION OF PHENOL RED

The phenol red clearance should not be confused with the familiar Rowntree and Geraghty 'phthalein test'. As with any other clearance, it is based upon the simultaneous determination of the concentration of the dye in the plasma (P) and the rate of its excretion (UV), and expresses the minimal volume of plasma required to supply the dye excreted in 1 min.

Apart from a limited number of observations by Marshall[1393] on the dog, the first systematic studies of the phenol red clearance were those of Shannon[1847] on this same animal, and of Goldring, Clarke, and Smith,[800] and Smith, Goldring, and Chasis[1939] on man.* Historically,

* MacKay[1884] injected 1 gm. of phenol red intravenously and calculated the Addis excretory ratio in three successive periods, and obtained values greatly in excess of the simultaneous urea values.

Workers in the writer's laboratory have shown that bromthymol blue and bromocresol red are excreted by the tubules in man. This work was abandoned when studies were begun on diodrast.

quantities of filtrate, and that the quantity of unbound or filtrable dye i inadequate on any acceptable estimate of the rate of filtration to account for the total quantity excreted in a given time. This paper affords the first acceptable demonstration of tubular excretion in the mammalian kidney.

The next year, Marshall and Crane[1399] showed that the rate of excretion, UV, does not increase in direct proportion to the plasma concentration, P, as is required for a substance excreted solely by filtration, but ultimately levels off and approaches a constant, maximal value. They suggested that the tubule cells became saturated at high plasma levels. Subsequently * Marshall[1393] showed that nearly 70 per cent of the phenol red in renal arterial blood may be removed in one circulati-- through the kidneys, a figure which was confirmed by Sheehan,[1873] wh further showed that the removal of dye is accompanied by concomitan excretion in the urine. Since only 25 per cent of the dye was free anc filtrable, the fact was inescapable that the rate of excretion was many times as great as could be explained by filtration alone.

A series of papers on the excretion of phenol red by the frog's kidney, in which tubular excretion was warmly debated, culminated in the acceptance of tubular participation by Richards, Bott, and Westfall[1811] in 1938. For references to these studies, see Forster.[675]

Phenol red is more extensively bound by plasma proteins than are diodrast and PAH. At a total concentration in human plasma of 1 mg/100 cc., only 20 per cent of the dye is unbound. Grollman[869,870] showed that it is the plasma albumin that combines with the dye, and that the equilibrium between unbound and bound dye is influenced by pH, temperature, etc. Under otherwise constant conditions, the combination between dye and protein in most species may be described by an adsorption isotherm, $x/m = Kc^{1/n}$, where x is the mg of dye absorbed by m gm. of albumin, c is the equilibrium concentration of unbound dye, and K and $1/n$ are constants. The theoretical deficiency of this equation has been discussed by Goldstein,[804] who justly recognizes that the problem should be treated as a stoichiometric phenomenon and not as a process of adsorption. The equilibrium between free and bound phenol red has been studied in man,[800, 1960] dog,[1847] rabbit (unpublished), chicken,[1628] and dogfish[1946] The values of $1/n$ for these species are,

* In the meantime, Marshall and Graflin[1409] had demonstrated the excretion of phenol red and other substances by the aglomerular kidney of the goosefish, *Lophius piscatorius*, the anatomy of which they had carefully re-examined to make sure that the entire kidney was lacking any sort of filtering device. In 1932, Chambers and Cameron[346] demonstrated the excretion of phenol red in *in vitro* cultures of the chick mesonephros

Goldring *et al*,[157] the phenol red clearance averaged 391 ± 85.5 cc. and the phenol red/inulin clearance ratio averaged 3.1 ± 0.34

The phenol red/inulin clearance ratio in Shannon's[1847] data on the dog averaged 1.7; this would give an approximate value for the phenol red clearance of 150 cc/sq. m.

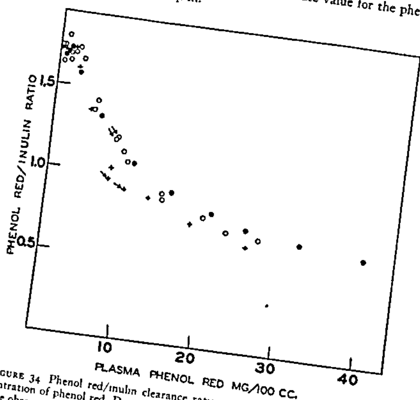


FIGURE 34 Phenol red/inulin clearance ratio in relation to total plasma concentration of phenol red Data on 3 dogs, each indicated by a different symbol The observations indicated by arrows were obtained during constant or increasing plasma concentration (Shannon [1847])

PHENOL RED Tm

The phenol red clearance in man is depressed, both absolutely and relative to the inulin clearance, by elevating the plasma concentration above the critical value (*c* 1.5 mg/100 cc) This depression of the clearance is a consequence of the fact that the tubular excretion of the dye is limited by a maximal rate, as in the case of diodrast, PAH, etc. Tm_{PR} in the

these investigations established two important points: the large magnitude of the phenol red clearance at low plasma levels, suggesting the possibility of developing methods for measuring the renal plasma flow; and the maximal rate of tubular excretion at high plasma levels.

PHENOL RED CLEARANCE AT LOW PLASMA LEVELS

To consider a specific example, a normal subject had an inulin clearance of 115 and a simultaneous phenol red clearance (P = 0.1 to 1.0 mg/per cent) of 402 cc/min. The phenol red/inulin clearance ratio was 3.5. The unbound phenol red at these plasma levels averaged about 20 per cent, and since only the unbound dye is filtrable, the filtration clearance of the dye was equal to 20 per cent of the inulin clearance, or 23 cc. It follows that the tubular clearance of the dye was 379 cc. (402 minus 23). Thus 6 per cent (23/402) of the total dye was excreted by filtration and 94 per cent by tubular activity. It is clear that the excretory capacity of the tubules is such that, despite a low filtration clearance occasioned by extensive protein binding, a considerable fraction of the dye entering the kidneys in the renal arterial blood is removed by the renal parenchyma and concomitantly excreted in the urine; i.e. the extraction ratio must be high.

Phenol red does not enter the red cells *in vitro*, though nothing is known about its behavior *in vivo*.[800]

The plasma extraction ratio of phenol red in man has not been measured directly, but it can be estimated from available data to be 0.5 to 0.6. Taking the extraction ratio of diodrast in man as 0.92 and the average phenol red/diodrast clearance ratio as about 0.60,[1935] the phenol red extraction ratio would be about 0.54. The average phenol red/inulin clearance ratio is 3.3, whereas the average diodrast/inulin clearance ratio is 5.26, indicating a phenol red extraction ratio of 0.63. Marshall obtained an extraction ratio of 0.70 in the dog, and Sheehan[1871] obtained 0.50 to 0.60. Whether this low extraction ratio is attributable to a limitation in tubular transport is not known. It seems possible that, as a result of extensive protein binding with consequent reduction of the unbound phenol red to some 20 per cent of the total, diffusion from the peritubular capillaries is retarded to such an extent that considerable blood escapes into the venous system before the dye is all cleared. A comparison of plasma binding and renal clearances of other sulphonephthaleins might clarify this problem.

The plasma phenol red clearance in 23 normal subjects, examined by Smith *et al.*,[1938] averaged 394 ± 45 cc.; the phenol red/inulin clearance ratio averaged 3.22 ± 0.25. In 29 additional subjects examined by

mesonephros, that phenol red is transferred from the peritubular fluid to the tubular lumen in a diffuse state and without accumulation in the vacuoles or granules of the tubule cells.[342] T_m in the dog is fairly constant; limited data give a value of about 8 mg/min. per 100 cc. of glomerular filtrate (fig. 35). Shannon's data on the action of phlorizin on the tubular excretion of phenol red are ambiguous.

SIMULTANEOUS EXCRETION OF PHENOL RED AND OTHER COMPOUNDS

When the plasma level of phenol red is elevated, the simultaneous diodrast clearance is depressed, even though the concentration of diodrast in the plasma is maintained below the level where self-depression begins. Similarly, elevation of the plasma level of diodrast or hippuran depresses the simultaneous phenol red clearance. Diodrast and hippuran have a powerful effect in depressing the phenol red clearance, whereas phenol red has only a moderate effect in depressing the diodrast clearance. This depression is again perfectly reversible; essentially the same phenol red/inulin clearance ratios are obtained when the concentration of diodrast or hippuran is allowed to fall from high levels as when it is rising from low levels, if appropriate correction is made for delay time (see fig. 32). The depression of the phenol red clearance is not a transient phenomenon, when the plasma concentration of diodrast is maintained at a high and constant level, the phenol red clearance is depressed to a low level, which is maintained steadily for 1 to 2 hr. An approximately equal degree of depression of the phenol red/inulin clearance ratio at the same plasma concentrations of diodrast and hippuran is observed in all normal subjects.

On the basis of the evidence above, it was concluded by Smith, Goldring, and Chasis[1338] that these compounds are excreted by a common cellular mechanism in the tubules and that, under conditions of overload with any one, quantitative competition to some extent excludes the compound of lowest affinity and concentration for tubular transport.

The instant reversibility of the depression of the phenol red clearance by diodrast or hippuran also shows that the last two compounds, like phenol red, are not stored or accumulated in the tubule cells during excretion.

Hippuric acid,* iopax, skiodan, and neoiopax have a similar depressive action on the phenol red clearance.[1449]

* The depression of the phenol red clearance by sodium hippurate (for which no adequate analytical methods were available) was the clue that led the author and his colleagues to study various hippuric acid derivatives and led to the introduction of p-aminohippuric acid.[1417] With due regard for the possibility of

only subject studied was 35.8 mg. (23 mg/100 cc. of glomerular filtrate).[1938]

Studies in the dog[1847] show that the self-depression of clearance is perfectly reversible; i.e. the phenol red/inulin clearance ratio traces the same course with ascending or descending plasma concentration (fig 34),

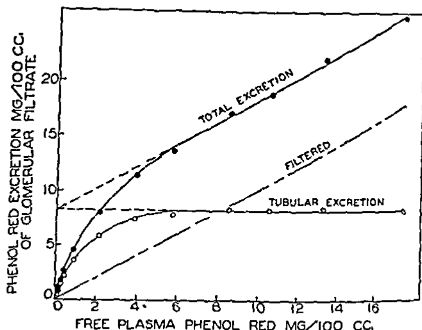


FIGURE 35 Excretion of phenol red in the dog in relation to the plasma concentration of unbound phenol red. The data are from a single experiment Tubular excretion of dye does not increase in direct proportion to P, but approaches and ultimately reaches an upper maximal limit. For this reason the total excretion by tubules and glomeruli does not increase in proportion to P; i e. the clearance, UV/P, is depressed as the plasma level of dye is raised above a critical value, as shown in figure 34. (Shannon[1847])

showing that there is no storage of dye in the tubule cells and that toxic phenomena are not involved * The conclusion that there is no storage in the tubule cells is fortified by the observation, in *in vitro* cultures of

* The lowest phenol red/inulin clearance ratio observed in man is about 0.20, which was reached at a plasma concentration of 70 mg/100 cc. of total phenol red. At this concentration of phenol red in the blood, the subject was a vivid pink.[1938] Phenol red, when properly purified, is relatively non-toxic, but only preparations specially prepared and tested should be used in large doses in animals or man.

mesonephros, that phenol red is transferred from the peritubular fluid to the tubular lumen in a diffuse state and without accumulation in the vacuoles or granules of the tubule cells.[440] Tm in the dog is fairly constant; limited data give a value of about 8 mg/min. per 100 cc. of glomerular filtrate (fig 35). Shannon's data on the action of phlorizin on the tubular excretion of phenol red are ambiguous.

SIMULTANEOUS EXCRETION OF PHENOL RED AND OTHER COMPOUNDS

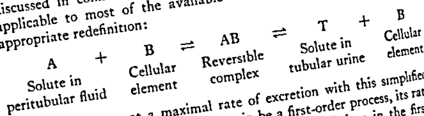
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Shannon's[1859] generalized hypothesis of tubular transfer, previously discussed in connection with the tubular reabsorption of glucose, is applicable to most of the available data on tubular excretion, with appropriate redefinition:



In order to arrive at a maximal rate of excretion with this simplified scheme, the second reaction must again be a first-order process, its rate slow in relation to the rate of attainment of equilibrium in the first. Were the second reaction faster than the attainment of equilibrium in the first, the rate of tubular excretion would be linearly related to plasma concentration It is conceivable that such could be the case with certain substances, as in the reabsorption of xylose, but at upper limits the rate of transport would be limited by the available energy in the tubule cell.* Further study may reveal that one type of limitation (rate of reaction) may be operating in some instances where there is a maximal rate of transport, and the other type (free energy limitation) operating in other instances.

The equation, based upon the law of mass action, which relates P_{PR}, T_{PR}, and T_{mPR} is

$$K = P_{PR} - \frac{T_{PR}}{RPF \frac{T_{mPR} - T_{PR}}{T_{PR}}}$$

where K is the equilibrium constant and RPF is the effective renal plasma flow as measured by the diodrast or other suitable clearance method.† ‡

enzymatic block or toxic action, this method or the substitution of PAH should afford a good means for testing for the tubular excretion of any substance sharing the tubular transport mechanism

* It may be significant in this connection that diodrast and hippuran displace phenol red from its combination with plasma protein.[1938] It is possible that a absorptive phenomenon on some common cellular protein is involved in tubula excretion The discussion of protein binding by Goldstein[304] is of interest in th connection.

† It has been remarked (p. 91), in connection with the application of Sha non's theory to tubular reabsorption, that the theory treats the entire kidne as a single nephron, and neglects the dispersion of glomerular activity on t one hand and of tubular perfusion on the other; i.e. all splay in the titrat curve is subsumed in the constant K. On the other hand, in the mathemat

The titration curve of phenol red differs from that of diodrast or PAH in that self-depression of clearance begins at a relatively low plasma concentration and long before T_{PR} reaches Tm_{PR}. This large splay in the titration curve of phenol red is unexplained.

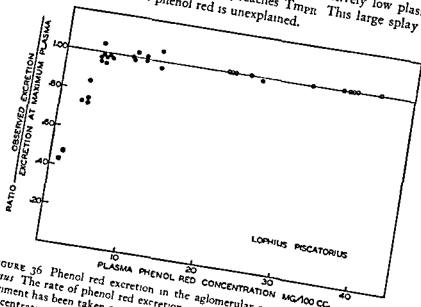


FIGURE 36 Phenol red excretion in the aglomerular goosefish, *Lophius piscatorius* The rate of phenol red excretion at the highest plasma level in each experiment has been taken as 1.0 and is plotted in relation to the observed plasma concentration as an open circle The rates of excretion in the periods prior to this have been plotted as the fraction of this value and are indicated by dots The rate of phenol red excretion has approximately reached a maximum at plasma concentrations of 6 mg/100 cc (Shannon [1887])

A maximal rate of tubular excretion of phenol red has been demonstrated in both aglomerular and glomerular kidneys,[1402] while Bieter [159] reported that the efficiency of the aglomerular kidney of the toadfish

analysis of the titration curve, as developed by Smith *et al* [illegible] (ch xv), each nephron in the case of glucose reabsorption, or each tubular unit (cell?) participating in tubular excretion, is presumed to effect complete transfer of the material available to it until saturation occurs This is equivalent to giving K a very large value, so that the titration curve of each reabsorptive or excretory unit generates a very sharp angle, and interpreting any observed splay as due to differences in the relative volume of carrier to the transfer units It seems reasonable to expect that a resolution of these conflicting interpretations can be effected experimentally.

‡ This equation has been applied to the tubular excretion of phenol red in the dog [illegible] and creatinine in the dogfish and chicken [illegible]

in excreting both creatinine and phenol red is markedly lower after a large dose than a small one. Shannon[1857] found average values of TmPR in the goosefish (fig. 36) and toadfish as 9 3 and 13.6 mg/day per kg, respectively. Limited information on *Opsanus* shows that, at high plasma concentrations, the concentration of unbound dye in the plasma may be greater than that in the urine, showing that the renal tubule is im-

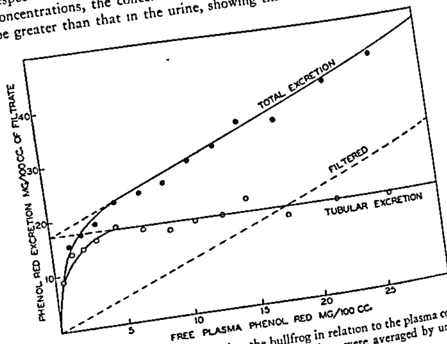


FIGURE 37. Excretion of phenol red in the bullfrog in relation to the plasma concentration of free phenol red Individual observations were averaged by units of plasma concentration. (Forster[871])

permeable to the unbound dye in the sense that it does not permit diffusion to occur. Only through the active transport system can phenol red gain access to the lumen.

In the dogfish, *Squalus acanthias*,[1943] the phenol red clearance at low plasma levels averaged 1750 cc/day per kg; from the studies of several investigators the filtration rate appears to be about 80 cc/day per kg; the phenol red/inulin clearance ratio averages 22.5. Since the extraction ratio of phenol red cannot be greater than 1.0, no more than 4 per cent of the total renal plasma flow can be filtered through the glomeruli, and it is probably only half of this figure Some 99 per cent of the dye is excreted by the tubules. The average value of Tm PR is 18 mg/kg. of body weight, or 4.8 mg/gm. of kidney, per day. This is about 23 mg/100

cc. of glomerular filtrate. Hippuran, but not creatinine, depresses the tubular excretion of phenol red in the dogfish.

In the bullfrog, *Rana catesbiana*, the highest phenol red clearance at low plasma levels was 185 cc/hr. per kg; the filtration rate in this experiment was 27 cc/hr per kg. Under these conditions, some 97 per cent of the dye was excreted by the tubules. Tm_{PR} averages 120 mg/day

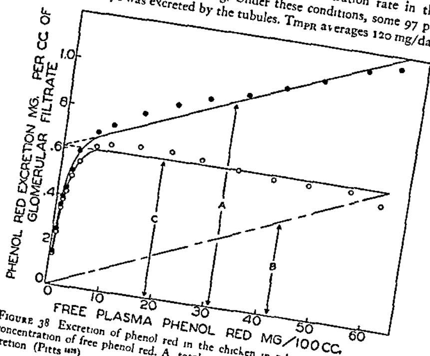


FIGURE 38 Excretion of phenol red in the chicken in relation to the plasma concentration of free phenol red. A, total excretion, B, filtered, C, tubular excretion (Pitts [1133])

per kg, or 0 18 mg/100 cc. of glomerular filtrate. Tm_{PR} is reached at plasma concentrations of unbound dye of 5 mg/100 cc (fig 37).

In the chicken,[1133] the phenol red clearance averages 36,000 cc/day per kg. or 25 cc/min per kg, the filtration rate 1 84 cc/min per kg or 18.7 cc/min per sq m The phenol red/inulin clearance ratio averages 13 Some 99 per cent of the dye is excreted by the tubules. Tm_{PR} averages 62 mg/100 cc of glomerular filtrate (fig 38) Phlorizin blocks the tubular excretion of dye, as shown by the reduction in the phenol red/inulin clearance ratio

In the perfused frog's kidney, the excretion of phenol red is independent of experimentally induced changes in the pH of the urine.

Neutral red, on the other hand, is copiously excreted into an alkaline urine, poorly into an acid urine. Kempton [1110] concluded that the movement of neutral red from blood to urine is a matter of diffusion, that of phenol red a matter of active transport.

The *in vitro* tubular excretion of phenol red by the teased nephrons of the flounder, *Pseudopleuronectes americanus*, has recently been put to excellent use by Forster [679] and Taggart and Forster [2039] in the study of enzymes and fuelstuffs involved in tubular transport.

Indigo carmine and azofuchsin are excreted by the aglomerular kidney and largely excreted by the tubules in the rabbit; cyanol is not excreted by the aglomerular kidney, and its excretion parallels but is less than that of inulin in the rabbit [405,659,1111] All these dyes are bound by plasma proteins, the extent of binding being difficult to determine because of adsorption upon collodion and other filters.

CREATININE

It is well established that, on a creatinine-free diet, muscle creatine and phosphocreatine are the only sources of urinary creatinine. The reaction creatine → creatinine is essentially irreversible, and creatinine administered intravenously in man is quantitatively excreted in the urine, though after oral administration a large fraction is lost in the intestinal tract.[634 635]

Of all ordinary substances that the kidney in man is normally called upon to excrete and for which common analytical methods are available, creatinine is concentrated to the greatest extent, i.e. it has the highest U/P ratio. This fact led Rehberg [1688] to suggest that the rate of excretion of exogenous creatinine could be used to measure the filtration rate. With Holten, Rehberg used the exogenous creatinine clearances in penetrating studies of renal function in health and disease [1030,1031] and a long list of papers has subsequently appeared, especially in the European literature, in which this clearance is equated with the filtration rate; these papers have afforded much valuable clinical information.

It should be noted particularly that Rehberg specified the use of *exogenous* creatinine. It has long been a matter of debate how much of the substance or substances in normal plasma which give the Jaffé reaction is actually creatinine, since all the chromogen is not absorbable on kaolin or Lloyd's reagent, as is creatinine. The problem is further complicated by Gaebler's [731] assertion that there

is present in dog and human blood a non-chromogenic substance, which is not creatinine but which yields creatinine after adsorption on Lloyd's reagent with subsequent elution with magnesium oxide. In the presumably specific enzymatic method,[1450, 1452] the endogenous creatinine in normal human plasma behaves like creatinine, but this method fails to distinguish between creatinine and the creatinoid compound formed in man when creatinine is administered, which is handled by the kidneys in a manner different from creatinine itself (*vide infra*).

Therefore, all investigators interested in the excretion of creatinine have administered it in sufficient quantities to raise the plasma level to 7 to 15 mg/100 cc. or higher, where the error caused by endogenous chromogen is small. All subsequent mention of the creatinine clearance refers to exogenous creatinine.*

Convincing evidence of the tubular excretion of exogenous creatinine was lacking when Rehberg made his suggestion, but shortly afterwards it was shown that creatinine is excreted not only by the aglomerular tubules of the goosefish[876, 1402] and toadfish,[1402, 1858] but also by the glomerular tubules of the dogfish,[891, 1844, 1845, 1860] teleost,[1625] and chicken.[1194, 1855]

Rehberg's inference has proved to be correct in the dog, in which the creatinine and inulin clearances are identical under all conditions,†[1721, 1846, 1849, 2093] and in the rabbit,[1090] sheep,[1851] seal,[1927] cat,[744] frog,[874] and turtle.[698]

The evidence for tubular excretion is as follows:

1. The creatinine/inulin clearance ratio, at low plasma levels of creatinine, ranges from 4.0 to 7.0 or above in the dogfish[1860] and the grouper.‡[1625] This ratio averages 1.54 in the chicken,[1855] and ranges from 1.1 to 1.48 in the orang-utan, gibbon, chimpanzee, baboon, and monkey.[1936]

Creatinine/inulin ratios in man averaging approximately 1.4 have been reported by Shannon,[1848] McCance and Widdowson,[1200]

* Various samples of creatinine may give different creatinine/inulin clearance ratios in man.[1864]

† A notable exception is the perfused dog kidney[1869] where tubular injury permits some loss of creatinine and possibly of inulin by diffusion from the tubular urine.

‡ Creatinine is stated not to depress the tubular excretion of phenol red in the dogfish but the single experiment is equivocal.[1848]

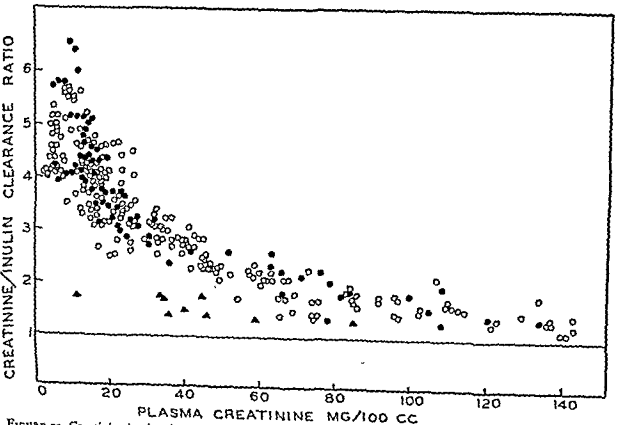


FIGURE 39. Creatinine/inulin clearance ratio in the normal dogfish, *S. acanthias*, as directly determined (solid dots) and recalculated from the creatinine/xylose clearance ratio (open circles). Triangles: after 200 mg/kg. of phlorizin intravenously. (Shannon [illegible])

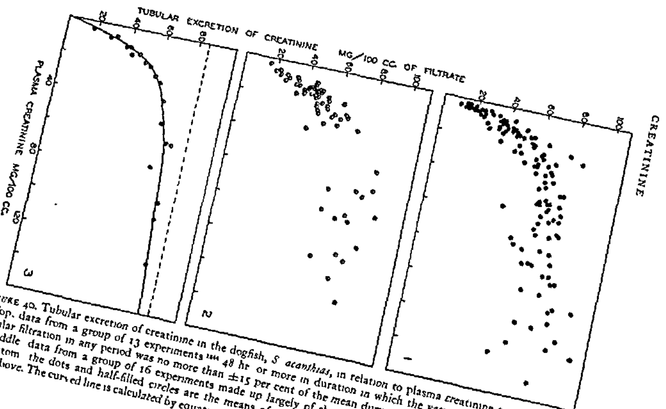


FIGURE 40. Tubular excretion of creatinine in the dogfish, *S. acanthias*, in relation to plasma creatinine concentration. Top. data from a group of 13 experiments[1844] 48 hr or more in duration in which the variation in the rate of glomerular filtration in any period was no more than ±15 per cent of the mean during the experiment. Middle data from a group of 16 experiments made up largely of short experiments which permit no selection.[1848] Bottom the dots and half-filled circles are the means of groups of experimental observations obtained from the data above. The curved line is calculated by equation (3), taking Tm = 84 mg/100 cc. of glomerular filtrate. (Shannon[1869])

Dean and McCance,[483] Josephson and Lindahl,[1085] Shannon Ranges,[1867] Odell,[1540] Josephson and Godin,[1084] and Brod and a,[264] and an average ratio of 1.25 is reported by Crawford.[445] hildren with the nephrotic syndrome and high inulin clear-

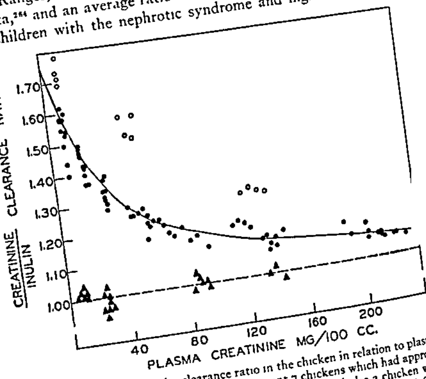


FIGURE 41. Creatinine/inulin clearance ratio in the chicken in relation to plasma creatinine concentration. The solid dots represent 7 chickens which had approximately the same maximum rate of tubular excretion, the circles a chicken with an aberrantly low filtration rate The smooth curve has been calculated from equation (3) taking Tm = 18 0 mg/100 cc of glomerular filtrate K has a value of 22 7. The derivation of this equation is discussed by Shannon.[1859] The triangles are creatinine/inulin clearance ratios after the intravenous administration of 200 mg/kg. of phlorizin (Shannon [1865])

ances, Emerson, Futcher, and Farr [605] report ratios from 1.33 to 1.76. Hogeman [1024] reports a correlation coefficient of 0.893 S.E. ± 0.16 between simultaneous inulin and creatinine clearances in 157 patients with a variety of renal and non-renal diseases. This correlation is better than between the inulin and urea clearances (0.818 S.E. ± 0.023). An average clearance ratio of 1.4 in man indicates that about 28 per cent (0.4/1.4) of the total creatinine in the urine is excreted by the tubules.

2. The creatinine clearance in all the above-mentioned species, including man, is depressed, both absolutely and relative to the inulin clearance, by raising the plasma level. This phenomenon in respect to tubular excretion in general is believed to be a consequence of the existence of a maximal rate of tubular excretion. Tm calculated for creatinine in the dogfish is 84, in the chicken 18, and

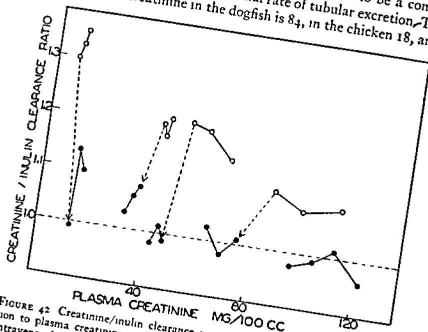


FIGURE 42 Creatinine/inulin clearance ratio in normal man (circles) in relation to plasma creatinine concentration Dots after 100 mg/kg of phlorizin intravenously (Shannon [1344])

in man about 13 mg/100 cc. of glomerular filtrate. Figures 39, 40, 41, and 42 show the creatinine/inulin clearance ratio in relation to the plasma creatinine concentration in these three species.*

3 The creatinine clearance is depressed relative to the inulin clearance by phlorizin, as is shown in figures 39, 41, and 42.

The excretion of creatinine in man requires special discussion. Shannon [1344] has shown that, immediately after the oral or intravenous

* In the toadfish, the excretion of creatinine increases with urine flow, a phenomenon not observed with phenol red The data indicate roughly that the maximal rate of excretion exists in this species and has a value of about 40 mg/kg of fish per day [1333]

administration of creatinine in doses sufficient to raise the plasma level to 7.3 to 10 mg/100 cc., the creatinine/inulin clearance ratio averages 1.39. As the plasma level is further elevated to 96 to 127 mg/100 cc., the mean ratio is depressed to 1.12.* At all plasma levels, phlorizin (100 mg/kg. intravenously) reduces the creatinine/inulin clearance ratio to 0.98 to 1.07. The facts that the creatinine/inulin clearance ratio at low plasma levels exceeds 1.0, that this ratio is depressed as the creatinine plasma

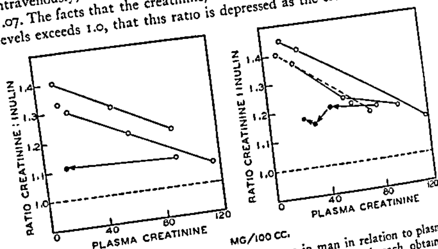


FIGURE 43. The creatinine/inulin clearance ratio in man in relation to plasma creatinine concentration. Circles: averages of 3 clearance periods each, obtained when the plasma concentration was increasing. Dots: averages of 3 clearance periods each, obtained after the plasma concentration had been raised and allowed to fall again. Points connected by lines represent observations on a single individual in 1 day. (Shannon [184])

level is raised, and that the ratio is reduced to approximately 1.0 by phlorizin, leave no doubt that creatinine is excreted by the tubules.

However, the excretion of creatinine in man is complicated by a factor not as yet reported in its excretion in other species or in the tubular excretion of other substances in man: namely, in other species the creatinine/inulin clearance ratio, after being depressed by elevation of the plasma creatinine level, rises again to its initial value as fast as the plasma level is reduced by excretion; this is the result to be expected

* Findley [44] failed to obtain self-depression of the clearance at plasma levels between 1.0 and 14 mg./100 cc. if he corrected for endogenous chromogen by deducting the arbitrary value of 0.5 from all plasma concentrations, and he has criticized Shannon's use of high plasma levels on the ground that they were beyond the 'physiological' range. In view of what is known now about tubular excretion, and the excretion of creatinine in particular, the criticism does not appear valid.

in terms of a reversible tubular transfer mechanism limited by a maximal rate, the reduction in the clearance ratio being simply an expression of the relative values of the numerator and denominator in the fraction $P_{CR}C_F/Tm_{CR}$. In man, however, the creatinine/inulin clearance ratio fails to rise as the plasma creatinine concentration is reduced by excretion, but remains for a number of hours at a value of 1.1 to 1.2 (fig 43).

Winkler and Parra [2228] subsequently observed that, following the ingestion of creatinine, both the creatinine clearance and the creatinine/sucrose ratio behaved erratically and generally fell as the experiment proceeded. They believed that the self-depression of the creatinine clearance at high plasma creatinine levels represented the same phenomena as the depression of the clearance with time. But Shannon and Ranges [1567] have presented evidence which appears to refute this interpretation. They have shown (a) that the creatinine/inulin clearance ratio does not fall markedly with time if the infusion of fresh creatinine is maintained, (b) that a second dose of creatinine elevates the depressed ratio toward the level characteristic of initial observations, and (c) that this elevation occurs only if the ratio is depressed by virtue of the prolonged circulation of creatinine in the body. These observations exclude 'fatigue' and 'stimulation' of the tubular excretory mechanism and accord with the supposition that, in the body, creatinine undergoes a change that makes it less readily excreted by the tubules The specific enzymatic method of analysis fails to disclose a significant amount of non-creatinine Jaffé-reacting material in plasma either before or after the administration of creatinine,[1450 1452] but the hypothetical transformation product need not give the Jaffé reaction; if it possesses a high affinity for a critical cellular excretory element and a slow rate of dissociation, minimal concentrations could compete with creatinine and reduce the tubular excretion of the latter at low plasma levels This competition would be alleviated by presenting more creatinine to the tubules by raising the plasma level.

Crawford [449] has shown that the creatinine/inulin clearance ratio is depressed to or toward 1.0 by the administration of large doses of diodrast or PAH, although the thiosulphate/inulin clearance ratio, normally averaging 1.0, is not altered under these conditions. She concludes that this phenomenon indicates a common mechanism for the tubular excretion of creatinine, diodrast, and PAH, and considers it additional evidence of the tubular excretion of creatinine in man. The depression of the creatinine/inulin clearance ratio in man by a high plasma concentration of diodrast is also evident in the data of Josephson.[1053] Bucht [285] reports that carinamide depresses the creatinine/inulin

clearance ratio for normal subjects from 1.24 ± 0.07 to 0.99 ± 0.04; in a few instances this ratio decreased under the action of carinamide below 1.0.

The tubular excretion of creatinine has not been accepted by all writers,[894] but is the only interpretation consonant with all the facts.

In a limited series of observations, Smith and Clarke[1936] found an average creatinine/inulin ratio of 1.48 in the orang-utan, 1.23 in the gibbon, 1.22 in the chimpanzee, 1.14 in the baboon, and 1.10 in the macaque monkey. The last two figures are equivocal, but Houck (pers. com.) has confirmed the observations in the macaque. It is to be concluded, therefore, that the anthropoid apes and monkeys resemble man in the matter of the tubular excretion of creatinine, a phenomenon unique among the mammals so far studied.

It seems surprising that the tubular excretion of creatinine should occur in some mammals and not in others, but such must be the conclusion on the basis of the evidence. Since the tubular excretion of creatinine is most highly developed in the fishes, one is tempted to view it as a primitive character and to believe that it persists as such in some of the higher animals and not in others. But its failure to appear in the frog and turtle argue against this interpretation. It is not impossible that this character has been acquired in the primates quite independently of any ancient heritage. Considerably more information must be gained on the comparative physiology of the kidney before questions such as this can be answered.

ENDOGENOUS CREATININE CHROMOGEN CLEARANCE

The apparent creatinine clearance based upon the endogenous substance or substances which yield color with alkaline picrate has been recommended as a measure of glomerular filtration in man.[644,1646,1647,2001]

The amount of chromogen present in plasma filtrates varies * considerably with the nature of the precipitating agent, even though the reagents have been demonstrated to give 100 per cent recovery with added creatinine.[1948] In man, the endogenous chromogen clearance had

* The average plasma concentration of endogenous chromogen in man ranges from 0.64 to 1.10 mg/100 cc. and is independent of protein consumption on a creatinine-free diet,[97 364] though the figure varies slightly with the type of analytical method used.

the same order of magnitude as the urea clearance when the Folin-W method of determination was used with a tungstate filtrate (whicl yields the highest chromogenic value);[373] this clearance is higher thar the inulin clearance with the iron filtrate, while with the tungstate filtrate the endogenous clearance as measured by the enzymatic method of Miller and Dubos[1450] was reported to be identical with the inulin clearance, thus behaving like true creatinine[1452] The difference between the two clearances is increased in subjects with nitrogen retention from renal disease. Non-creatinine chromogen in dog plasma remaining after absorption of creatinine by Lloyd's reagent has a very low clearance and, since it represents some 25 per cent of the plasma chromogen, it lowers the total chromogen clearance substantially.[1366] The endogenous chromogen clearance in the dog ranges from 38 to 48 per cent of the inulin clearance with the tungstate filtrate[1349] and from 48 to 63 per cent with the iron filtrate[1366] In infants this ratio averages 0.60 ± 0.066 (0.55 0 0 69)[264] In the rat, the endogenous chromogen clearance is about 25 r cent of the exogenous creatinine clearance[1343]

Creatinine is certainly among the endogenous chromogens in both dog and man but, with equal certainty, not all the chromogen is creatinine The clearance of the non-creatinine fraction is lower than the inulin clearance in both species and, therefore, it gives an erroneously low figure to the total chromogen clearance. In so far as creatinine tends to accumulate in man in consequence of renal retention, the apparent clearance will come to exceed the inulin clearance, as it should if the chromogen were all creatinine

Steinitz and Turkand,[2000, 2001] using the picric acid filtrate method of Popper, Mandel, and Meyer, and Steinitz' inulin method, report endogenous chromogen/inulin clearance ratios in 27 observations on 11 subjects without renal disease averaging 1 03 (0 73 to 1 17), whereas in subjects vith nephritis this ratio ranged from 1.04 to 1 73 On determination of the endogenous chromogen and exogenous creatinine clearances sequentially in 22 subjects, they obtained an endogenous chromogen/exogenous creatinine clearance ratio averaging 1.22 (0 85 to 1.87). Their data, and those reported by others,[264] leave no doubt concerning the difference between the clearances of exogenous creatinine and endogenous chromogen or the fact that the endogenous chromogen is closer to the inulin clearance than the true creatinine clearance.

The observations of Steinitz and Turkand have received confirmation in the recent studies of Brod and Sirota,[264] who have used a modified (1:4) Folin-Wu tungstate filtrate and the Bonsnes and Taussky creatinine method They report that the endogenous chromogen/inulin

clearance ratio in 14 normal subjects averaged 1.00 ± 0.018 (range 0.88 to 1.10). The chromogen/thiosulphate clearance ratio averaged 0.95 ± 0.018 (0.80 to 1.01). Inulin or mannitol clearance ratios close to 1.0 are also encountered in the reports of Aas and Blegen,[2] Blegen et al.,[194] Eder (pers. com.), Lundquist,[1294] Sinclair-Smith et al.,[1902] Sims and Seldin,[1901] and Emerson, Futcher, and Farr,[605] though in all instances the deviation is sometimes large, possibly because the analytical method for chromogen was not so accurate as that used by Brod and Sirota. As in the work of Steinitz and Türkand, Brod and Sirota found that, when determined sequentially, the endogenous chromogen clearance is lower in the same subject relative to the inulin clearance than is that of exogenous creatinine. In 13 subjects with renal disease studied by Brod and Sirota, with a single exception these clearance ratios averaged 1.04 ± 0.109 (0.89 to 1.25) and 1.10 ± 0.292 (0.77 to 1.63). The discrepancy between the chromogen and inulin clearances of 10 per cent or greater appeared only in patients with filtration rates below 40 cc/min. The exception noted was a young female in the nephrotic stage of glomerulonephritis; in this instance the chromogen was excreted in a manner similar to exogenous creatinine, the chromogen/inulin clearance ratio averaging 1.61, the chromogen/thiosulphate clearance ratio 1.60, the first value checking at 1.65 after 5 weeks. Two gm of carinamide orally every 4 hr. for 8 doses, as well as plasma levels of 60 mg/100 cc. of PAH, had no effect on the chromogen/inulin clearance ratio except in the subject in whom this ratio was normally 1.61. Carinamide lowered the ratio to 1.07, providing additional evidence of tubular excretion of chromogen (creatinine?) in this subject.

Brod and Sirota note that the absolute difference between the chromogen and inulin clearances, even in renal disease, is so small that the chromogen clearance can be used as a clinical test of the filtration rate in the adult. This recommendation should be subject to reservations, however. A discrepancy of 60 per cent was found consistently in one of their patients and an equal discrepancy in the opposite direction is present in all infants, while conditions involving excessive protein metabolism, which raise the plasma chromogen,[255] have not been examined. Moreover, contrary to Brod and Sirota's inference, Baldwin, in the writer's laboratory, using the same plasma filtrate and analytical method, finds that in 11 subjects with congestive cardiac failure the ratio averages 0.84 (range 0.65 to 1.03). The endogenous chromogen/inulin clearance ratio may be as high as 1.3 or higher in recovery from carbon tetrachloride intoxication[1903] and in chronic glomerulonephritis,[2] and is unreliable in such conditions. Blegen, Haugen, and Aas,[193] usin

the Folin-Wu method, which seems rather less reliable than the Bonsnes-Taussky method, report an average endogenous chromogen clearance in 37 normal individuals of 105 ± 21 cc. (67 to 163); in 40 normal individuals the average chromogen/urea clearance ratio was 1.55 ± 0.37, in 30 cardiac patients 1.63 ± 0.35, and in 36 patients with renal disease 1.92 ± 0.48. In 37 normals the average inulin clearance was 126 ± 25, the average chromogen/inulin clearance ratio 0.84 ± 0.14; in 27 cardiac patients this value was 0.84 ± 0.16, a ratio identical with that of Baldwin. In 13 cardiac patients and 2 normals the average chromogen/thiosulphate clearance ratio was 0.89 ± 0.13. They note that, in view of the close correlation between the urea clearance (equal to 4 + 0.58 x chromogen clearance) and of the fact that the chromogen clearance is independent of diuresis and easier than the urea clearance to determine, the chromogen clearance has some clinical advantages.

Brod and Kotátko[268] have more recently separated 'true'(?) endogenous creatinine from non-creatinine chromogen by adsorption of the former on Lloyd's reagent, and find that 'true' creatinine comprises about 75 per cent of total chromogen. Contrary to the experience of Brod and Sirota, Brod and Kotátko obtained a total chromogen/inulin clearance ratio below 1.0 in several normal subjects. In all but one instance, the clearance ratio using 'true' creatinine was 1.0. Carinamide and high plasma levels of PAH had no effect on this ratio, and they believe that 'true' endogenous creatinine is excreted without tubular reabsorption or excretion. The non-creatinine chromogen has a low clearance and reduces the total clearance in proportion to its concentration. In chronic renal disease, the 'true' creatinine/inulin clearance may rise to 2.2 and is depressed by carinamide and PAH toward 1.0, and the authors suggest that the excess creatinine clearance in chronic renal disease is an indicator of the number of hypertrophic(?) and aglomerular nephrons(?).

Sirota, Baldwin, and Villarreal[1103] obtained an average chromogen/inulin clearance ratio of 0.95 ± 0.10 (range 0.75 to 1.09) in 9 subjects studied over a period of 24 hr. They note, however, that significant variations in the plasma concentration of chromogen may occur throughout the day and night, which exceed the changes to be expected from changes in filtration rate, assuming constant creatinine production. Hence plasma concentrations of chromogen should be determined at 4 to 6 hr intervals if the chromogen clearance is to be used to measure glomerular activity throughout a 24-hr period or longer.

Hare, Goldstein, Barnett, McNamara, and Hare,[811] using an absorption-elution (Lloyd's reagent) method of Hare and Hare,[814] report in

24 observations on 22 normal subjects from 1 week to 40 years of age, each involving 3 to 9 clearance periods, an average 'true' creatinine/inulin clearance ratio of 1.03 (0.82 to 1.26). The average exogenous creatinine/inulin clearance ratio in 9 experiments on 6 normal subjects (76 periods) was 1.08 (0.97 to 1.20). The authors conclude that some 80 per cent of the chromogen in normal serum is creatinine, 90 per cent or more in chronic renal disease. In renal disease, both the endogenous and exogenous chromogen/inulin clearance ratios increase to 1.29 to 2.64. No comment is made on the per cent of 'true' creatinine in plasma some hours after the administration of creatinine.

IMPERMEABILITY OF THE TUBULES

Some of the investigations referred to above throw considerable light upon an important question in renal physiology, namely, the extent to which various substances may escape from the tubular urine by diffusion in consequence of the high concentration gradient established by the reabsorption of water. Shannon[1844,1845] found that there is no detectable difference between the creatinine and inulin clearances in the dog (0.993 ± 0.048), even when the urine flow is very low (U/P ratios up to 574). The diffusion coefficient of creatinine is 5 times as large as that of inulin; if as little as 2 per cent of the inulin contained in the glomerular filtrate diffused back through the tubules, one would expect the back diffusion of 10 per cent of the filtered creatinine, which would create a detectable difference in the clearances. Since no such difference is observed, one must conclude that the tubules of the dog are relatively impermeable to both inulin and creatinine, and we may justifiably extend this conclusion to those animals in which creatinine is excreted in part by tubular excretion, especially in view of the identity of the creatinine and inulin clearances after phlorizin.

Shannon and Winton[1868] have shown that the identity of the creatinine and inulin clearances is maintained in dogs anesthetized with chloralose (100 mg/kg. intravenously) at U/P ratios from 22 to 196, but in the isolated perfused dog kidney the creatinine/inulin clearance ratio begins to fall when the inulin U/P ratio exceeds 40 and reaches 0.85 at inulin U/P ratios from 65 to 159. The creatinine clearance is lower than the inulin clearance only when the inulin U/P ratio is high, and not when, at a correspondingly low arterial pressure and low urine

flow, the U/P ratio is prevented from rising by urea diuresis. The that the deficit in the creatinine clearance is not easily interprete a result of passive diffusion of creatinine, and they believe that creatinine lost may be an incidental constituent of some of the r sorbed fluid, when the tubular reabsorption of water approaches c pleteness.

From the results above, and from estimates of the permeability the tubules to urea (see p. 75), it is clear that the renal tubules in t intact animal have a high degree of impermeability.

IOPAX (UROSELECTAN)

2-oxo-5-iodopyridine-N-acetic acid

The excretion of iopax has been examined in only 2 subjects In one, the iopax/inulin clearance ratio at plasma iodine concentrations of 3 0 to 4 4 mg/100 cc. averaged 4 26 In the second subject, this ratio at 0 64 to 0 70 mg/100 cc. iopax iodine averaged 5 7. The clearance is self-depressed, Tm having a value in the 2 subjects of about 27 and 21 mg. of iodine (0 21 and 0 17 mM) per min Iopax depresses the phenol red/inulin clearance ratio in a manner similar to diodrast [1049] Simultaneous and successive clearances in the dog show that the iopax clearance is 65 to 80 per cent of the p-hydroxyhippuric acid clearance and therefore of the diodrast clearance (table 11) [1937] It is clear that iopax is excreted by the tubules, that the extraction ratio at low plasma levels is large, though not as large as that of diodrast, and that a common tubular mechanism is involved in the excretion of iopax and phenol red Data on plasma protein binding are available,[1960] and studies on excretion in the chicken by Lambert [1194]

NEOIOPAX

N-methyl-3,5-diiodo-4-pyridoxyl-2,6-dicarboxylate

In one subject the neoiopax/inulin clearance ratio at 1 0 mg/100 cc iodine in the plasma averaged 1 24, this ratio was depressed at 0 99 at 12 mg/100 cc plasma iodine In a second subject, the clearance ratio averaged 1 15 at 5 mg/100 cc iodine and was depressed to 0 80 at 41 mg/100 cc. iodine. FW was calculated to be 0 72 to 0.89 at these concentrations. Neoiopax depresses the phenol red/inulin clearance ratio, but less markedly than does iopax or diodrast. Tm is of the order of 3 mg iodine (0 01 mM) per min It is concluded that neoiopax is slightly, but poorly, excreted by the tubules [1049] Data on plasma protein binding are available [1960]

2-PYRIDONE-1-ACETIC ACID

Simultaneous and successive observations in the dog show that this compound is cleared at about the same rate as p-aminohippuric acid and, therefore, diodrast.[1937] It is essentially the nucleus of diodrast and iopax, differing from both in the absence of iodine and from diodrast in the position of the oxygen. It can be concluded that the presence of iodine is not responsible for the high extraction ratio of diodrast, but that this is a function of the nuclear structure.

SKIODAN

mono-iodomethane sulphonate

Elsom, Bott, and Shiels [600] *reported that the skiodan clearance* averaged 93 per cent of the creatinine clearance in the dog, and that the ratio of these clearances was independent of the plasma concentration of skiodan. Landis, Elsom, Bott, and Shiels [1206] reported skiodan/creatinine clearance ratios in man ranging from 0.82 to 1.14 and averaging 0.95. Smith and Ranges [1949] found an average skiodan/inulin clearance *ratio in 2 subjects of 1.2, this ratio being* slightly depressed by elevation of the plasma skiodan concentration. Since at 1.0 mg/100 cc. of skiodan iodine only 82 per cent of the skiodan in human plasma is filtrable,[1950] it appears that there is slight tubular excretion. This conclusion is supported by the facts that skiodan depresses the phenol red/inulin clearance ratio and that it is excreted by the aglomerular toadfish kidney.[600]

P-AMINOPHENYLSUCCINIC ACID

The p-aminophenylsuccinic acid clearance in the dog is initially greater than the creatinine clearance and increases erratically on prolonged infusion, indicating metabolism to some substance with a high clearance value.[1937]

PENICILLIN

Rantz and Kirby [1676] have shown that penicillin is excreted by the tubules in man, the clearance having an order of magnitude of 750 to 1000 cc. of plasma per min. Infusion of penicillin in quantities up to 20,000 units failed to establish a maximal rate of tubular excretion. The clearance is unaffected by the urine flow. Beyer, Peters, Woodward, and Verwey [145] showed that the penicillin clearance in dogs is essentially the same as the PAH clearance, and Beyer, Miller, Russo, Patch, and Verwey [142] report that penicillins G, K, F, and X have essentially similar renal clearances at low plasma levels (0.4 to 0.9 units/cc.) in the dog, the

values ranging from 200 to 300 cc/min., the average creatinine/penicillin clearance ratios ranging from 0.29 to 0.35, indicating that the extraction ratios are as high as that of PAH Jensen *et al.*[104] report penicillin/creatinine ratios greatly in excess of 1.0 in the rabbit, the dog, and man

In man, Eagle and Newman [552] find that penicillins F, G, and X have clearances ranging from 550 to 900 cc/min, the inulin/penicillin clearance ratio ranging from 0 18 to 0 31, indicating again nearly as high an extraction ratio as with PAH, so that the clearances are maximal, or approximately equal to the renal plasma flow The clearances were independent of the absolute blood level over the range 0.05 to 10 micrograms/cc., and independent of urine flow. Urinary recovery of these three penicillins is practically 100 per cent, whereas recovery of penicillin K is only some 30 per cent. Penicillin K in man had a clearance only one-fourth to one-half that of F, G, or X In rabbits, the average clearance values for penicillins F, G, and X were, respectively, 32, 56, and 36 cc/min., figures comparable to the renal plasma flow Single intravenous injections of 600 mg/kg of penicillin G (corresponding to 60 million units in the average human adult), sufficient to yield plasma levels of 2667 to 3200 microgram/cc , appeared to saturate the tubular excretory mechanism, since the clearance was depressed to the level of the filtration rate.

Eagle and Newman point out that attempts to modify the rate of excretion of penicillin by reducing the urine flow either by water restriction or the use of pitressin are physiologically unsound. The rate of clearance is independent of urine flow and would be affected only by measures reducing the renal blood flow

Eagle and Newman [555] suggested that, because of the wide range of penicillin that can be established without self-depression of clearance, it would be superior to diodrast and PAH for measuring the renal blood flow, and Bryner, Randall, and Rantz [286] have utilized injections of penicillin in beeswax and peanut oil for this purpose in 31 subjects, generally repeating the test on separate days; the difference between the two clearances was high, with an overall average of 29 5 per cent. Part of this difference is attributable to the fact that the determination of penicillin, depending as it does on a bioassay and serial dilution technique, has an error of −20 to +40 per cent.

Rammelkamp and Bradley [182] showed that the tubular excretion of penicillin is depressed by diodrast, and Beyer and his coworkers showed that it is depressed by PAH; the latter recommended the use of PAH to reduce the penicillin clearance and maintain the plasma concentration

for therapeutic purposes.[139 145, 150 1262] Carinamide (*vide infra*) is, however, superior for this purpose. The oral administration of benzoic acid is much less effective than PAH or carinamide because it is excreted as rapidly as it is conjugated to form hippuric acid.[202]

CARINAMIDE *

Carinamide (4′-carboxyphenylmethane sulfonanilide), or 'staticin,' was shown by Beyer and his coworkers [139, 142] to depress the tubular excretion of penicillin. This inhibitory action is exerted equally on the tubular excretion of penicillins G, K, F, and X, and the resulting reduction in the penicillin clearance elevates the plasma concentration obtained with a given dose of antibiotic.[436, 454, 2111] Carinamide is without adverse effects, the action on the renal tubules being reversible, and it is effective when administered orally or parenterally At suitable doses, the inhibition of tubular excretion is almost complete, the penicillin/creatinine ratio being depressed below 1 0 (0.7 to 1 0) in the dog because of plasma binding of the penicillin.

Brod and Kotátko [262] have shown that moderate doses of carinamide, sufficient to depress Tm_{PAH} if this value is normal, do not depress C_{PAH} as measured at low plasma levels If Tm_{PAH} is reduced, the same dose of carinamide will depress C_{PAH} without affecting the inulin or endogenous creatinine chromogen clearance. Their evidence supports the belief that carinamide competes with PAH in the tubular transport system. Where the tubules are intact, large quantities of carinamide are required to block PAH excretion; in the presence of renal disease small quantities are effective.

Carinamide depresses the tubular excretion of PAH and phenol red at both low and high plasma concentrations of these compounds, but has no effect on glucose Tm, arginine Tm, or the urea, sulfonamide, or creatinine clearances. In doses sufficient to suppress completely the tubular excretion of penicillin, it did not influence significantly the heart or respiratory rate, systemic blood pressure or kidney volume, and proved to be relatively non-toxic.[141 148, 203]

Beyer and his coworkers [139, 142, 143] estimated that the rate of excretion of carinamide (UV) was that to be expected from the rate of administration and the creatinine clearance, and concluded that it is excreted exclusively by filtration This led Beyer to suggest that it depressed tubular excretion by specifically blocking the enzyme system involved in tubular transport,[139] and not by competition for the transport system, as has been accepted for other substances that show material interference

* Originally spelled caronamide

in tubular excretion. But Earle and Brodie,[543] having developed an analytical method for carinamide, reported that 40 per cent is protein-bound in dog plasma at a drug concentration of 10 mg/100 cc. and an albumin content of 3.5 gm/100 cc. The uncorrected renal clearance in the dog they found to be approximately one-half the filtration rate but, when corrected for plasma binding, the ratio of the clearance to the filtration clearance was 1.30. They concluded that carinamide excretion involves tubular excretion, and that the depression of the penicillin, phenol red, diodrast, and PAH clearances represents competition within the tubular transport system, as in other cases.

Beyer and his colleagues,[149, 1883] exploring further into what appears to be a complicated problem, affirm that considerable amounts of carinamide and of its metabolites are reversibly adsorbed on plasma protein. The carinamide and total carinamide/creatinine clearance ratios are depressed by elevation of the plasma concentration, but never exceeded 1.0 at any plasma concentration. PAH at high plasma concentrations reduces both clearance ratios. The authors believe that a large portion of the drug filtered through the glomeruli is reabsorbed by the renal tubules; however, at low plasma concentrations filtration of the drug as calculated from the unbound fraction cannot account for the total rate of excretion. They propose (a) that plasma binding, or the electrostatic attraction between plasma protein and carinamide, impedes the amount of drug filtered on a temporal basis but does not limit filtration to the unbound drug as determined in a static *in vitro* system, alternatively, (b) that both tubular excretion and reabsorption occur. The inhibition of excretion by PAH may be reconciled with either hypothesis, although sufficient evidence to establish either interpretation is not available.

PHENOLSULPHURIC ESTER

Whereas the phenol clearance in the goat is about 20 per cent of the creatinine clearance, phenolsulphuric ester and phenol glucoronide have clearances about three times as great as the creatinine clearance.[1872]

UROBILIN

In dogs, the urobilin/creatinine clearance ratio ranged from 0.53 to 1.35 and averaged 1.03. In man, this ratio ranged from 0.95 to 1.86 and averaged 1.48. The authors conclude that in the dog it is excreted by filtration only, but that in man tubular excretion raises the clearance above even that of creatinine. The urobilin clearance is greatly reduced in patients with renal disease.[1780]

ATABRINE

The atabrine/PAH clearance ratio had a value of 0.1 at a urine pH of 7.6 in 2 subjects, increasing to 0 6 at pH 6 0. The data indicate that atabrine is excreted by the tubules, but that *the free base diffuses or is* actively reabsorbed into the blood.[605]

TETRAETHYLAMMONIUM

The quaternary nitrogen ion, tetraethylammonium, when infused into the renal artery of the dog, has an estimated extraction ratio of 58 to 73 per cent, or better than twice the simultaneous creatinine extraction ratio. The extraction ratio approaches that of creatinine at plasma concentrations of 4 to 6 mg/100 cc, and, at higher concentrations, may fall below that of creatinine. Plasma protein binding has not been studied.[1695]

N^1-METHYLNICOTINAMIDE

This quaternary ammonium compound (NMN) is a principal metabolic product of nicotinic acid and is excreted after the administration of either nicotinic acid or nicotinamide. Sperber (*vide infra*) first called attention to its tubular excretion in the chicken kidney. Beyer, Russo, Gass, Wilhoyte, and Pitt[146] have shown that it is excreted by the tubules in the dog, the creatinine clearance ratio at low plasma levels being close to 3 0. The clearance is self-depressed on elevation of the plasma level, but Tm was not determined because of a toxic action accompanied by nausea and vomiting, hemolysis, and hematuria There is slight if any binding by plasma proteins. NMN does not depress the PAH clearance or Tm_{PAH}, while PAH does not depress the NMN clearance or NMN/creatinine clearance ratio The NMN clearance is not depressed by nicotinamide (a tertiary amine which is reabsorbed by the tubules) or carinamide under conditions in which the latter compound completely suppresses the tubular excretion of penicillin and greatly depresses the PAH clearance. The NMN clearance is not depressed by trigonelline (N-methylnicotinic acid) or 1-methyl-3-carboxylamide-6-pyridone (a metabolite of nicotinamide) in the concentrations studied.

The data agree with Sperber's conclusion that the excretion of NMN is effected by a different mechanism in the tubules than is involved in the excretion of hippuric acid and its derivatives (and therefore diodrast and phenol red and the penicillins). Beyer *et al.* suggest that the NMN mechanism may be common to the quaternary bases.

The authors point out that in mice the acute intravenous toxicity of nicotinic acid is 1170 ± 143 mg/kg., while nicotinamide is still less toxic ($LD_{50} = 2100 \pm 155$ mg/kg.). Since the amide is an essential metabolite, it is consistent that its renal elimination should be very low, i.e. that it should be reabsorbed by the tubules. In the inactivation of nicotinamide by transmethylation, however, the toxicity is increased sixfold (LD_{50} of NMN $= 345 \pm 26$ mg/kg.). Thus, the tubular excretion of NMN would seem to be a compensatory measure for the increased toxicity of this non-essential metabolite of nicotinamide. Except in the dog, NMN excretion represents a small percentage of the total dose of nicotinamide administered, by far the greater amount of nicotinamide metabolite is believed to be a pyridone or other degradation product. Thus it seems that in the metabolism of nicotinamide, the body makes use of both renal tubular excretion of a toxic product plus, in some species, a further oxidation of the amide to less toxic products whose rates of renal excretion are of less importance. Consistent with this interpretation is the observation that the acute intravenous LD_{50} of the 6-pyridone derivative in mice is 1310 ± 80 mg/kg., or roughly one-fourth that of its probable precursor (NMN).[144]

TUBULAR EXCRETION OF OTHER SUBSTANCES IN THE CHICKEN KIDNEY

Reference has been made to the tubular excretion of phenol red, uric acid, and creatinine in the chicken kidney. Sperber[1970, 1971, 1972] has qualitatively examined the excretion of other substances in the chicken by injection into one leg vein. Because the renal-portal circulation is unilateral, tubular excretion accelerates the rate of excretion on the injected side relative to the control. He finds that hippuric acid, ornithuric acid, p-acetylaminobenzoic acid, methyl glucuronide, phenylglucuronide, phenol sulphuric ester, and probably resorcinylglucuronide are all excreted by the tubules, while free phenols, benzoic acid, p-aminobenzoic acid, glucuronic acid, and probably pregnanediol are not. He emphasizes that the substances susceptible to tubular excretion are products of important detoxication mechanisms. The excretion of the phenolic glucuronides is depressed by hippuric acid. N-methylnicotinamide, piperidine, guanidine, and methylguanidine are also excreted by the tubules, but this process is not depressed by hippuric acid or diodrast. His studies, with those of Beyer *et al.* cited above, indicate that at least two transport mechanisms are involved in tubular excretion.

chemically this compound is more like creatinine than uric acid.

Allantoin excretion in the rat is increased by the administration of a number of physiologically active substances,[1403] some of which may transiently increase the filtration rate while others may increase purine metabolism.

HEXITOLS

The excretion of hexitols was first studied by Smith, Finkelstein, and Smith,[1948] using a periodate oxidation method on plasma filtrates and urines, the plasma filtrate having been treated with yeast to remove glucose and other fermentable substances. In the dog, the sorbitol/creatinine clearance ratio averaged 0.97, the sorbitol/inulin ratio 0.97, the mannitol/creatinine ratio 0.94, the mannitol/inulin ratio 0.96, the dulcitol/creatinine ratio 0.98, and the sorbitan/creatinine ratio 1.00.

In man, the sorbitol/inulin clearance ratio averaged 1.01, the mannitol/inulin ratio 0.99, the dulcitol/inulin ratio 0.94, and the sorbitan/inulin ratio 1.01. None of these ratios was considered to differ significantly from 1.0.

Thus the three hexitols, sorbitol, mannitol and dulcitol, and the first anhydride, sorbitan, appeared to be excreted without tubular reabsorption. They represented the first compounds whose clearances checked the inulin clearance in man.*

Earle, Taggart, and Shannon,[565] using the periodate method, obtained a mannitol/inulin clearance ratio, in 8 subjects with various degrees of renal disease, ranging from 0.92 to 1.03 and averaging 0.96, and Selkurt *et al*[1827] obtained an average mannitol/creatinine ratio of 0.97 in 16 periods in the dog. Subsequently, however, Berger, Farber, and Earle[123] were led to re-examine the excretion of mannitol in man, using the chromotropic acid method of Corcoran and Page,[425] in which glucose does not react and which therefore does not require that the plasma be treated with yeast. They obtained an average mannitol/inulin clearance ratio of 0.87. A similarly low ratio has been reported by Corcoran and Page[425] in both man and dogs, by Hoobler (quoted by Corcoran and Page) in

* When procurement of pyrogen-free inulin became impossible during the war, mannitol was substituted in the author's laboratory for measuring the glomerular clearance in clinical investigations,[1117,1676] and it came into widespread use. In reviewing clearance data, the writer has quoted uncorrected mannitol clearances unless otherwise stated

man, and by investigators in the writer's laboratory (unpubl. obs.) when the chromotropic acid method is used. It has been found in the writer's laboratory that there is apparently something in mannitol as now commercially available which is removed by yeast if the yeast has been washed and stored in the icebox for several days (as was commonly the practice), whereas freshly washed yeast does not remove it; and the clearance ratio is higher when the plasma is yeasted with stored yeast, presumably because of removal of this fermentable substance. It would seem that this substance is also reabsorbed by the renal tubules. Hence, whether a clearance ratio of 0 9 or 1 0 is obtained depends in part upon whether or not yeast is used, and upon the fermenting activity of this yeast, which not only varies after washing but is not the same in all samples of yeast Moreover, Kendrick, Swisher, and Forrest[1113] show that, during yeast fermentation of glucose, a significant quantity of material (3 to 4 per cent), presumably glycerol, is formed which reacts in the periodate method, and that failure to correct for this error reduces the mannitol clearance value In view of these difficulties, mannitol is no longer considered suitable for the clinical measurement of the filtration rate, and other hexitols should not be used for this purpose without re-examination of the foregoing sources of error.

The second anhydrides, isomannide and sorbide, are reabsorbed to a great extent, the creatinine clearance ratios in the dog being 0.47 and 0.55 respectively.[1444] Saturation of the glucose mechanism (P_G = 428 to 458 mg. per cent) does not significantly change the isomannide/creatinine clearance ratio. Sorbitol, mannitol, isomannide, and sorbide were shown to be completely ultrafiltrable from plasma.

Sorbitol is metabolized to a considerable degree, and only 32 per cent of a measured intravenous dose was recovered in the urine in man when the simultaneous inulin recovery was 98 per cent. Dulcitol and mannitol are apparently only slightly metabolized; 87 per cent of a measured dose of dulcitol was recovered in man in 10 hr. (no inulin reference), and 81 and 89 per cent of mannitol were recovered in 10 5 hr as compared with 95 and 97 per cent recovery of inulin[1444] Some investigators have denied that mannitol is metabolized in man, but the majority agree that it is[122,1048,1509]

Sorbitol, mannitol, dulcitol, and isomannide have been demonstrated to be relatively non-toxic, and sorbitol[1507] and isomannide[1156] have been recommended as osmotic diuretics.*

* Mannitol has been widely used to maintain the urine flow at practical values during clearance studies in both the dog and man For this purpose a

Newman, Bordley, and Winternitz[1513] have attempted to determine renal clearances by the intravenous injection of single doses of mannitol, and they have related such clearances to the apparent volume of distribution of mannitol as calculated from the falling plasma curve, a volume they identify, with reservations, as close to that of the extracellular fluid. The errors inherent in using rapidly changing plasma levels for the determination of clearances, and the impossibility of determining the extracellular fluid volume by a single injection of any substance which has a substantial clearance rate, have been discussed in chapter III.

GLYCEROL

Glycerol excretion begins in man at plasma concentrations of about 10 mg/100 cc. The general relations between P and UV are such as to suggest tubular reabsorption with a maximal rate, but in the absence of simultaneous measurements of the filtration rate this inference cannot be accepted as established.[2026]

POLYETHYLENE GLYCOLS

Shaffer, Critchfield, and Carpenter[1943] have studied the excretion in the dog of polyethylene glycols ranging in molecular weight from 400 to 6000. Those with average molecular weights of 400, 1000, 1540, and 4000 are cleared from the plasma at a rate identical with that of creatinine. The ratio of the clearance of the polyethylene glycol of average molecular weight of 6000 to that of creatinine is consistently less than 1.0 (0.6 to 0.8); the clearance ratio is unaffected by extreme hyperglucemia or by saturation of the tubules with diodrast. It seems unlikely that it is reabsorbed by passive diffusion, since it is the least diffusible of those studied. It is more likely that the clearance deficit is due to the failure of filtration of a very elongate molecule. The polyethylene glycols appear to be distributed in the extracellular fluid, and those of a lower molecular weight are metabolized to a limited extent

FRUCTOSANS

Beattie and Corcoran[116] report that levan polysaccharides having a molecular weight between 7000 and 8000 show an initial creatinine clearance ratio of 0.7 to 1.0 when either injected in a single dose or con-

5 per cent mannitol solution carrying such other solutes as are desired may be given intravenously at the rate of 2 cc/min in the dog and 4 cc/min in man, following a priming injection of some 300 mg/kg of body weight. Precautions concerning the use of any substance as an osmotic diuretic in anuria are discussed in chapter XXIV.

tinuously infused, but the clearance ratio declines to 0.2 to 0.4 by the end of the second hour.

Frisin, which has a molecular weight of about 23,000, shows initial lower clearances (creatinine clearance ratio of 0.60 to 0.85), but the clearance also decreases with time, even on continuous infusion.

These fructosans are probably not homogeneous, and the decrease in clearance on continuous infusion might be interpreted, according to Corcoran, as due to occlusion of glomerular 'pores'

FERROCYANIDE

Ferrocyanide is one of the few substances tested that is not excreted by *the aglomerular kidney except in traces* *[1392] *Investigators have long* used its excretion as an easy test to determine whether a fish is aglomerular or not. Van Slyke, Hiller, and Miller[2093, 2096] and more recently Berliner, Kennedy, and Hilton[133] report that the simultaneous ferrocyanide, inulin, and creatinine clearances in the dog are equal, but Miller and Winkler[1453] found that in man the ferrocyanide clearance is at the level of the urea clearance, or usually about half of the creatinine clearance, and they conclude that about 40 per cent of the filtered ferrocyanide is reabsorbed by the tubules. They point out that this might be due to a specific difference in the kidney of man and dog, or [illegible] Miller and Winkler was impure and contained a toxic factor. The problem would invite further investigation in man were it not for the adverse renal and other effects obtained by these investigators, which prescribe considerable caution.

THIOSULPHATE

Gilman, Philips, and Koelle,[781] by the use of the single injection method, found that the thiosulphate and creatinine clearance are identical in the dog and concluded that thiosulphate is excreted only by filtration. Only 70 to 80 per cent of intravenously injected thiosulphate was recovered in the urine; the loss for the most part

* Gersh and Stieglitz[771] concluded that there is no reabsorption of ferrocyanide by the tubules of the rabbit kidney, but their evidence was based upon the histochemical demonstration of this substance in the capsular fluid and lumen of the tubules, and its absence from the tubule cells, in kidneys which had been rapidly dehydrated at low temperatures. Such evidence must be considered qualitative and equivocal

occurred during and immediately following injection and only slow destruction was noted after equilibration was complete. The lost moiety is largely oxidized to sulphate. Such thiosulphate as escaped destruction was distributed approximately in the extracellular fluid.

Pitts and Lotspeich,[1642] using the infusion method, confirmed Gilman *et al.* in finding a thiosulphate/creatinine clearance ratio averaging 1.00 (0.90 to 1.13), this identity being preserved at plasma thiosulphate concentrations ranging from 17.8 to 55.6 mg/100 cc. The administration of thiosulphate was without effect upon the creatinine and PAH clearances and, since this salt lacks buffering activity, it has no effect upon the excretion of titrable acid, differing importantly from creatinine in this respect and offering some advantages in studies of acid-base equilibrium.

Newman, Gilman, and Philips[1514] reported the thiosulphate/inulin clearance ratio in man (sex unspecified) to average 0.99 ± 0.08 (0.7 to 1.3), this ratio being independent of plasma thiosulphate concentration between 6 and 60 mg/100 cc. in various patients, and independent of urine flow. All data were, however, obtained by the single injection method. There is some metabolism of thiosulphate in man, as in the dog The identity of the thiosulphate/inulin clearance ratio has been confirmed in man (sex not stated) in various renal diseases by Brun,[272] and by Crawford[449] in 7 women at plasma concentrations of 10 to 25 mg/100 cc. Blegen, Ørning, and Aas[194] obtained a thiosulphate/inulin clearance ratio of 1.08 ± 0.13 at plasma thiosulphate concentrations averaging 15 mg/100 cc. in 2 normal subjects and 13 patients with heart disease, and cautiously note that the deviation from 1.0 'may be accidental,' while Bjørneboe, Dalgaard-Mikkelsen, and Raaschou[180] report that in 3 subjects (sex unspecified) the thiosulphate/inulin clearance ratio is higher when the urine is alkaline than when it is acid.

In view of the general concord, the mechanism of thiosulphate excretion would appear to be settled as one of pure filtration. Bing and Effersøe[169] report that in rabbits the thiosulphate/creatinine clearance ratio (excluding 2 anomalous tests in which the ratio was below 1.0) averaged 0.999, this ratio being independent of plasma concentration between 1.9 and 274 mg. per cent, and of urine flow In cats, however, at low plasma thiosulphate concentrations (9 to 30 mg/100 cc.) these investigators find that the thiosulphate/creatinine clearance ratio has a value of 1.2 to 2.5, and averages about 1.9; the ratio is depressed as the plasma thiosulphate concentration is increased, being about 1.3 at 100

mg/100 cc. and approaching 1.0 at 200 mg/100 cc. or higher. The same results were obtained on a rising and falling plasma thiosulphate c[illegible] centration, and show no conspicuous relation to the absolute value the creatinine clearance or urine flow. The authors conclude that in ca[illegible] thiosulphate is excreted by the renal tubules. Tubular excretion als[illegible] occurs in kittens which have had no food other than mother's milk.[illegible] Eggleton and Habib [illegible] confirm these observations in cats, and believe that it is possible to demonstrate a maximal rate of tubular excretion.

Lambiotte, Blanchard, and Graff,[illegible] observing that thiosulphate clearances in pregnant women were much higher than the published data on inulin and mannitol, have re-examined the thiosulphate/inulin clearance ratio in pregnant and non-pregnant women and in dogs. In pregnant women this ratio invariably exceeds 1.0 (range 1.01 to 2.12), the ratio being greater (1.25) at low (4 to 15 mg/100 cc.) than at high levels (1.08 at 26.5 mg/100 cc. and above). These investigators also demonstrate that the ratio is depressed by carinamide to the range of 0.78 to 0.85. In the pregnant dog, the ratio was only slightly above 1.0 (1.12) but after carinamide it averaged 0.76. PAH at high (Tm) plasma levels also depresses the ratio below 1.0 in both non-pregnant women and dogs. Lambiotte *et al.* conclude that thiosulphate is both excreted and reabsorbed by the tubules, tubular excretion being depressed by carinamide and PAH. In their view, previous studies have been made at such fortuitous plasma concentrations as to yield an inulin or creatinine ratio of 0.9 to 1.1 merely by coincidence. Because the absolute value of the thiosulphate clearance is lower in non-pregnant women and dogs than during pregnancy, they infer that tubular excretion (or reabsorption) is modified by endocrine activity.

Bucht [illegible] reports that after carinamide, the thiosulphate/inulin clearance ratio in human subjects (sex unspecified) is lowered from 1.36 ± 0.29 to 0.81 ± 0.11. In these experiments the plasma level of thiosulphate was maintained at about 18 mg/100 cc. He finds that the clearance ratio is depressed from 1.68 at plasma levels of thiosulphate below 10 mg/100 cc., to 0.76 at plasma levels above 35 mg/100 cc. This author also believes that the excretion of thiosulphate involves both tubular excretion and reabsorption.

The usefulness of the thiosulphate clearance must therefore remain in doubt.

HEXAMETHYLENETETRAMINE

The hexamethylenetetramine/creatinine clearance ratio in the dog averages 0.76 (0.70 to 0.82) at plasma concentrations ranging from 56 to 561 mg/100 cc. The hexamethylenetetramine/xylose clearance ratio

averages 0.986. After phlorizin (355 mg/kg.) the hexamethylenetetramine/creatinine ratio remained unchanged (0.763 as compared with 0.761), while the xylose/creatinine ratio rose from 0.764 to 0.957.

It is clear that hexamethylenetetramine is reabsorbed by the tubules, but not by the glucose reabsorptive mechanism. Adequate data are not available on the effect of urine flow upon the hexamethylenetetramine/creatinine clearance ratio, but the fact that this ratio is independent of plasma concentration over so wide a range of the latter suggests that the reabsorptive process is a passive rather than an active one. It should be remembered, however, that the xylose/creatinine clearance ratio is scarcely affected beyond the experimental error by comparable plasma changes, and one cannot at the present time confidently exclude an active process.[1626]

THIOUREA AND ITS DERIVATIVES

Thiourea, methylthiourea, phenylthiourea, and s-diethylthiourea are reabsorbed in the dog, apparently by passive diffusion as is urea, since the creatinine clearance ratios all diminish with decreasing urine flow. Thiourea is handled almost exactly like urea, the thiourea/urea clearance ratio on decreasing or slowly increasing rates of urine flow averaging 1.007 ± 0.07. The clearances are independent of plasma concentration within the physiological range At normal low rates of urine flow, the methylthiourea clearance ratio averages about 0.50, the phenylthiourea/urea clearance ratio 0.20, and the s-diethylthiourea/urea clearance ratio about 0.03. Thiourea shows an anomalous increase in clearance (exaltation) when the urine flow is accelerated, as does urea,[1850] a phenomenon which apparently represents solute abstracted from tubule cells (or interstitial fluid) when the distal urine is suddenly diluted at the onset of diuresis. This phenomenon, however, is not shown by the thiourea derivatives. The authors relate the relative reabsorption of these compounds to their lipoid solubility (ratio of the solubilities in water and ether), urea and thiourea being least, and phenylthiourea most lipoid soluble.[369, 1522]

Thiourea is only slightly reabsorbed, apparently by diffusion, by the tubules of the dogfish, *S acanthias*, although urea, which is actively reabsorbed in the Sub-class Elasmobranchii, may have a *U/P* ratio as low as 0.10[291]

SULFONAMIDES

All the sulfonamides and all the naturally conjugated derivatives that have been studied are extensively bound by plasma albumin, reducing their availability for filtration. To be significant, clearances and

clearance ratios must be corrected for this plasma binding, which is highly variable between species, and even in human plasma in health and disease *[144, 147, 676, 861, 865, 804, 1892]

Compounds with a free amino group in the *para* position of the benzene ring (which includes all therapeutically active sulfonamide compounds) are conjugated by the liver (and spleen) in the rat, cat, rabbit, and man, presumably largely by acetylation, as is the case with p-aminobenzoic acid and p-aminohippuric acid. p-Amino conjugation has never been demonstrated in the dog.[1937, 1400, 2015, 2016, 2015, 2101] The evidence indicates that conjugation does not occur in the kidney.[1130, 2008] Conjugation varies markedly in different rabbits, perhaps because of variations in hepatic blood flow. By covering the reactive p-amino group, the compound is removed from colorimetric determination by the Bratton and Marshall[214] method, so that no error is thereby introduced into the clearance determination. But some sulfonamides (ex. sulfapyridine) are otherwise metabolized without conjugation in the p-amino position,[1318] and in so far as this occurs the Bratton and Marshall method will measure a mixture of unknown nature in plasma and urine and clearances do not reveal how the original compound is handled by the kidney. The error from this source is probably small, but may contribute to variability in clearance depending on how long the material has been in the body, the hepatic blood flow, and the velocity of metabolism.

In brief, it may be said that the unconjugated sulfonamide compounds have clearances which, corrected for plasma protein binding, are less than the filtration rate in dog and man; that these clearances are variable and slightly influenced by the rate of urine flow, more markedly by the rate of electrolyte excretion and particularly the pH of the urine; and that both passive and active reabsorption possibly contribute to the clearance deficit. The acetylated compounds have clearances which, if corrected for plasma protein binding, frequently exceed the filtration rate and involve tubular excretion, these clearances are also variable and probably influenced to some extent by the factors listed above.

In the dog, the uncorrected sulfanilamide/creatinine clearance ratio was shown by Marshall, Emerson, and Cutting[1401] to have a value of 0.20 to 0.30. The clearance ratio is independent of plasma concentration

* The determination of plasma protein binding is open to large errors, and it is desirable to control all ultrafiltration or dialysis experiments by including some unbound constituent, such as creatinine, starting from concentrations both above and below equilibrium values where dialysis is used. The ultrafiltrate/plasma ratio of creatinine at equilibrium should be equal to 1.0/W, where W is the per cent of protein-free water in the plasma.

averages 0 986 After phlorizin (355 mg/kg.) the hexamethylenetetramine/creatinine ratio remained unchanged (0.763 as compared with 0.761), while the xylose/creatinine ratio rose from 0.764 to 0.957.

It is clear that hexamethylenetetramine is reabsorbed by the tubules, but not by the glucose reabsorptive mechanism Adequate data are not available on the effect of urine flow upon the hexamethylenetetramine/creatinine clearance ratio, but the fact that this ratio is independent of plasma concentration over so wide a range of the latter suggests that the reabsorptive process is a passive rather than an active one. It should be remembered, however, that the xylose/creatinine clearance ratio is scarcely affected beyond the experimental error by comparable plasma changes, and one cannot at the present time confidently exclude an active process.[1626]

THIOUREA AND ITS DERIVATIVES

Thiourea, methylthiourea, phenylthiourea, and s-diethylthiourea are reabsorbed in the dog, apparently by passive diffusion as is urea, since the creatinine clearance ratios all diminish with decreasing urine flow. Thiourea is handled almost exactly like urea, the thiourea/urea clearance ratio on decreasing or slowly increasing rates of urine flow averaging 1 007 ± 0.07. The clearances are independent of plasma concentration within the physiological range At normal low rates of urine flow, the methylthiourea clearance ratio averages about 0.50, the phenylthiourea/urea clearance ratio 0.20, and the s-diethylthiourea/urea clearance ratio about 0.03 Thiourea shows an anomalous increase in clearance (exaltation) when the urine flow is accelerated, as does urea,[1850] a phenomenon which apparently represents solute abstracted from tubule cells (or interstitial fluid) when the distal urine is suddenly diluted at th onset of diuresis This phenomenon, however, is not shown by th thiourea derivatives The authors relate the relative reabsorption these compounds to their lipoid solubility (ratio of the solubilities water and ether), urea and thiourea being least, and phenylthiour most lipoid soluble.[369 1522]

Thiourea is only slightly reabsorbed, apparently by diffusion, by tubules of the dogfish, *S acanthias*, although urea, which is acti reabsorbed in the Sub-class Elasmobranchii, may have a U/P rati low as 0 10.[391]

SULFONAMIDES

All the sulfonamides and all the naturally conjugated derivatives have been studied are extensively bound by plasma albumin, r ing their availability for filtration To be significant, clearance

clearance ratios must be corrected for this plasma binding, which is highly variable between species, and even in human plasma in health and disease.* [144, 147, 478, 881, 458, 804, 1692]

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from 5 to 50 mg/100 cc., but increases during diuresis. A creatinine clearance ratio of 0.20 in dogs was obtained by Green, Allison, and Morris.[847] In rabbits the clearance is 30 to 40 per cent of the creatinine or inulin clearance.[1371]

In man, the uncorrected sulfanilamide clearance ranges from 20 to 50 cc.[1401,2049] Loomis, Koepf, and Hubbard[1372] obtained a mean uncorrected sulfanilamide/inulin clearance in 25 subjects of 0.45. The conclusion of Marshall *et al.* that the sulfanilamide clearance is dependent on urine flow was confirmed by Stewart, Rourke, and Allen,[2007] but not by Loomis *et al.*[1372] and Green, Allison, and Morris.[847] The question requires further investigation in relation to water diuresis by means of clearance ratios.

Marshall and Litchfield[1408] report an average uncorrected sulfapyridine/creatinine clearance ratio in the dog of 0.26. In man, sulfapyridine has an uncorrected clearance of 11 to 42 cc. in the data of Taylor, Lowell, Adams, Spring, and Finland.[2049] Frisk[772] reported average uncorrected creatinine clearance ratios in man as: sulfanilamide 0.3 to 0.5, sulfapyridine 0.2, sulfathiazole 0.5, and sulfamethylthiazole 0.16. In a subsequent report[773] Frisk records that the uncorrected sulfamethylthiodiazole clearance is close to that of creatinine, whereas the sulfacarbamide, sulfaguanidine, sulfathiazole, N^1-dimethylacrylsulfanilamide, sulfamethylthiazole, sulfaethylthiodiazole, sulfapyridine, and sulfapyrimidine clearances are less than that of creatinine. Lindahl and Josephson[1341] report average inulin clearance ratios as: sulfanilamide 0.40, sulfapyridine 0.22, and sulfathiazole 0.40. The sulfamethylthiodiazole clearance was as great and sometimes greater than the inulin or creatinine clearance.

Beyer, Peters, Patch, and Russo[141] report the average creatinine clearance ratio, corrected for plasma binding, for the four unconjugated sulfonamides in the dog as: sulfamethiazine 0.07 to 0.13, sulfamerazine 0.13 to 0.30, sulfadiazine 0.22 to 0.49, and sulfathiazole 0.30 to 0.51; in all instances alkalization of the urine with sodium bicarbonate increased these figures, the ratio in the case of sulfathiazole rising to about 1.0; and in all instances the clearance ratio increased with urine flow. Within a narrow range, however, the ratio was not affected by the plasma concentration of the sulfonamide.

Earle[681] found that the sulfamerazine/inulin clearance ratio in man, corrected for plasma binding, averaged 0.150, the sulfadiazine/inulin clearance ratio, also corrected, 0.348 (4 subjects each). Studies on the excretion of sulfamerazine over a wide range of plasma concentrations (2 to 43 mg/100 cc.) in the dog gave no evidence of a maximal rate of

reabsorption, and excretion was not modified by the infusion of casein hydrolysate or benzoic acid. But increased excretion accompanied augmented electrolyte excretion after the administration of sodium, potassium, and ammonium chlorides, during sodium sulphate diuresis, and during pitressin antidiuresis (when electrolyte excretion is increased), indicating that tubular reabsorption may be associated with sodium reabsorption. Earle notes that it is difficult to understand how passive diffusion could account for the reabsorption of as much sulfamerazine as is indicated by an average (corrected) clearance ratio of 0.15.

The data of Strauss, Lowell, Taylor, and Finland[2014] show uncorrected sulfathiazole clearances in man ranging around 50 cc. and of sulfamethylthiazole around 20 cc., while those of Reinhold, Flippin, Schwartz, and Domm[1464] indicate an uncorrected clearance for sulfadiazine of 12 to 56 cc. Subsequently, Reinhold, Flippin, Domm, Zimmerman, and Schwartz[1463] report the average corrected sulfonamide/inulin clearance ratio as sulfapyridine (5 subjects) 0.28 ± 0.08, sulfathiazole (6 subjects) 0.87 ± 0.15, sulfadiazine (8 subjects) 0.31 ± 0.11, and sulfamerazine (7 subjects) 0.20 ± 0.07. The last figure was not significantly different (0.20 ± 0.06) in 4 patients with renal disease whose inulin clearances were between 40 and 78 cc/min. The clearance ratio of sulfathiazole implies that there is little tubular reabsorption of this compound in man, as in the dog.[844] The administration of these compounds appeared temporarily to reduce the urea clearance. The uncorrected clearance of glucose sulfapyridine is higher than that of sulfapyridine, but no clearance ratios are available.[2049]

Becker-Christensen and Schou[118] report that during sulphate diuresis in the rabbit the sulfathiazole clearance rises to values above the creatinine clearance, from which they argue that this compound is excreted by the tubules.

ACETYLATED DERIVATIVES

As in the case of the unconjugated sulfonamides, the excretion of the acetylated compounds is complicated by plasma protein binding. In general, however, from both uncorrected and corrected clearances, it appears that in most instances excretion involves tubular participation. Frisk[722] reported that the naturally conjugated sulfanilamide, sulfapyridine, sulfathiazole, and sulfamethylthiazole had higher clearances (uncorrected) in man than the unconjugated compounds. He found this to be generally true for other compounds.[723] In contradiction of these observations, Lindahl and Josephson[1111] report that in man the conjugated derivatives of sulfanilamide, sulfapyridine, sulfathiazole,

and sulfamethylthiodiazole had lower clearances than the unconjugated compounds, confirming this by the administration of the acetyl derivatives of the last two compounds.

However, Loomis *et al.*[1371] report that the uncorrected acetylsulfanilamide, inulin, and creatinine clearances in the rabbit are practically identical, the acetylsulfanilamide clearance being independent of plasma concentration and urine flow; and Loomis, Koepf, and Hubbard[1372] report that the uncorrected acetylsulfanilamide/inulin clearance ratio in 25 human subjects averaged 1.03; however, the arithmetic average of the difference between the clearances was 20.6 cc., or nearly one-half the mean. Earle[561] showed that the acetylsulfamerazine/inulin clearance ratio in 4 subjects, uncorrected for plasma binding, averaged 0.490, but when corrected for plasma binding this ratio averaged 2.42 (range 1.59 to 3.11), showing extensive tubular excretion. The naturally conjugated derivatives, called acetyl derivatives by Reinhold *et al.*,[1897] had the following inulin clearance ratios in man: R-sulfapyridine 0.23 ± 0.14 (uncorrected for plasma binding); R-sulfathiazole (corrected) 2.17 ± 1.18; R-sulfadiazine (corrected) 0.82 ± 0.64; R-sulfamerazine (corrected) 1.6 to 6.4. The uncorrected creatinine clearance ratios of acetylsulfamerazine, acetylsulfamethazine, acetylsulfadiazine, and particularly acetylsulfathiazole are increased in the dog by alkalinization of the urine and by diuresis to values near or above 1.0.[147]

An extensive study of a variety of sulfonamides with respect to plasma protein binding and creatinine clearance ratios has been carried out by Fisher, Troast, Waterhouse, and Shannon.[668] Their data afford valuable information on the relation of chemical structure to tubular reabsorption, tubular excretion, and distribution throughout the body fluids. Those compounds with polar-non-polar configuration appear to be excreted by the tubules, while non-polar molecules, with few exceptions, are not.

Lundquist[1284] believed that sulfathiazole and sulfamethylthiodiazole are excreted by the tubules in man, but, though his uncorrected clearances are in general agreement with those reported by others, his estimates of plasma binding (84 and 94 per cent, respectively) appear to be in error in being too high (45 per cent is the figure quoted for sulfathiazole by Reinhold *et al.*[1892]). Lundquist's assertion that the gross sulfathiazole and sulfamethylthiodiazole clearances are markedly depressed relative to the inulin clearance by the intravenous administration of hippuran invites confirmation. It may be that a multiple system of tubular excretion and reabsorption may be involved in the excretion of some of these compounds, as appears to be the case with potassium, thiosulphate, and carinamide, or it may be that the acidification of the urine which occurs

when hippuran is administered influences sulfonamide excretion.* His observations on the excretion of p-aminobenzoic acid fail to take into account the rapid conjugation of this compound with glycine in the body to form PAH, the excretion of which is depressed by other compounds excreted by the tubules

In connection with the demonstration by Beyer *et al.*[illegible] that alkalinization of the urine diminishes the tubular reabsorption of several sulfonamides, it is of interest that sulfanilamide and other compounds inhibit the acidification of the urine, an effect attributable to inhibition of carbonic anhydrase [illegible]

P-AMINOBENZOIC ACID

The p-aminobenzoic acid clearance in the dog shortly after the initial priming injection is less than the creatinine clearance, indicating tubular reabsorption (plasma binding was not studied), but on prolonged infusion the clearance rises to high values, indicating conjugation to p-aminohippuric acid, which has a physiologically maximal clearance.[illegible]

P-AMINOMANDELIC ACID

The p-aminomandelic acid/creatinine clearance ratio in the dog averages 1 07; the mannitol clearance ratio (using the periodate method) in man averages 0 94 The deviations between this clearance and that of mannitol, especially in long experiments, indicate that the compound is slightly metabolized, as is mandelic acid, which is in part degraded in man to L-phenylaminoacetic acid, benzoylformic acid, and benzoic acid [illegible]

SALICYLIC ACID

Salicylic acid is conjugated in both dog and man with glycine to form salicyluric acid, and with glycuronic acid Salicylic acid itself is heavily bound by plasma proteins The mixed excretion of conjugated and unconjugated acid is a function of urine pH, the clearance having a low value in acid urine (5 to 10 cc/min), increasing at pH 6 0 to approach the thiosulphate clearance at pH 7 0 The proportion of unconjugated acid in the urine increases from some 15 per cent at pH values below 6 0 to 40 per cent at pH 7.5 Apparently the excretion of unconjugated acid does not exceed the filtration rate below pH 7 3, indicating tubular reabsorption, while at pH values above 7.3 there is evidence of tubular excretion Administration of bicarbonate does not effect plasma binding.[illegible] It seems probable that conjugated salicylic acid products, and particularly salicyluric acid, are excreted by the tubules, as in the case of hippuric acid, etc , and that the effect of bicarbonate is on the reab-

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sorption of unconjugated salicylic acid. Unconjugated salicylic acid appears to have a clearance about equal to that of urea in man.[1236]

p-Aminosalicylic acid is similarly conjugated,[2182] and it is highly probable that this compound and p-aminosalicyluric acid would be excreted like salicylic and salicyluric acid, the high inulin clearance ratios reported in man [1034] remaining ambiguous until differentiation between the compounds is made

STREPTOMYCIN

Streptomycin, an antibiotic obtained from *Actinomyces griseus*, has been shown by Adcock and Hettig [7] and Marshall [1397] to have a clearance (30 to 80 cc.) below that to be expected by filtration. Plasma protein binding was not examined

By the single injection method, Boxer, Jelinek, and Edison [220] obtained a streptomycin clearance in the dog averaging 69.5 ± 8.4 per sq. m., in man 69 5 ± 13.7 cc. per 1.73 sq. m. The clearance was independent of urine flow and plasma level. The streptomycin/thiosulphate clearance ratio in the dog averaged 0 70. The authors demonstrate that about 3c per cent of the drug is bound to plasma protein and conclude that when the data are corrected for this factor, streptomycin is excrete solely by filtration without tubular reabsorption.

BACITRACIN

The antibiotic, bacitracin, derived from *B subtilis* Tracy, had a clearance in 9 normal subjects between 105 and 283 cc. (average 159). In 8 rabbits the clearance varied from 2 to 7 cc. (average 4.1). Although these figures are close to established filtration rates, the bacitracin/thiosulphate clearance ratio varied from 0.52 to 1 83 (average 1.1) in 8 subjects, possibly because of technical errors or impurities.[680]

Bacitracin has proved to have, or to contain an impurity which has, a nephrotoxic action. Michie, Zintel, Ma, Ravdin, and Ragni [1448] have shown that the repeated administration of therapeutic doses produces moderate to severe renal damage, as indicated by variable albuminuria and a reduction in filtration rate, E_{PAH}, PAH clearance, Tm_{PAH}, and phosphate Tm. The effects appear to be largely reversible. Immediate detrimental action following single doses was not clearly demonstrable. Miller, McDonald, and Shock [1463] found in 12 subjects who received 1500 units of bacitracin per kg. on two successive days that 24 to 48 hr. later (at the time of maximal proteinuria) Tm_{PAH} was decreased by 15 to 85 per cent (average 39 per cent), while Tm_G was decreased by

20 to 76 per cent (average 52 per cent) Both values returned gradually over a period of 3 to 8 weeks to 88 per cent or more of the control values in 10 of 12 subjects. In the other 2, Tm_{PAH} was still depressed by 25 per cent at 8 weeks The filtration rate and PAH clearance were depressed by an average of 32 and 24 per cent, respectively, and tended to recover more rapidly than did the Tm values.

CINCHONINIC ACID

Cinchoninic acid and some of its derivatives are of particular interest because of their capacity to inhibit the excretion of phenol red by the tubules of frog kidney slices *in vitro*.[486] 3-Hydroxy-2-methyl, 3-hydroxy-2-phenyl, and 6-methoxy cinchoninic acid are more active than carinamide in this respect, while the 2-phenyl derivative (cinchophen) is about equally active with carinamide These compounds are metabolized, and it is not clear whether or not the components involved in tubular excretion include conjugated derivatives. (Marshall, pers com.)

CITRIC ACID

The citric acid/creatinine clearance ratio was less than 0.03 in 5 dogs, 0 12 in a sixth. In some instances the oral administration of citric acid (6 to 10 gm) increased this clearance ratio, in other instances it had no effect. In every instance tried, sodium and potassium bicarbonate increased the clearance ratio, with or without an increase in plasma citrate concentration Regardless of the procedure, when the plasma citrate increased significantly, tubular reabsorption increased; when plasma citrate was not increased, tubular reabsorption remained the same or decreased [982]

ORGANIC BASES

The excretion of nicotine $pK_a' = 8\ 07$),[832] quinine ($pK_a' = 8\ 3$),[833] quinacrine ($pK_a' = 7\ 67$), chloroquine ($pK_a' = 8\ 06$), and santoquine [1068] is increased in acid urine, decreased in alkaline urine. The reasonable interpretation is that in alkaline urine a sufficient quantity of free base is present to permit extensive back diffusion.*

CHORIONIC GONATROPHIN

Chorionic gonatrophin in 4 pregnant women had a renal clearance averaging 0 38 cc. (σ less than 0 20) with no significant deviation in the first,

* If the principle is accepted it may also be applicable to the excretion of ammonia

second, or third trimester. This clearance in a woman with a degenerating remnant of a hydatidiform mole was 0.22 and 0 42 cc. preoperatively and 0 32 on the first day postoperatively; the hormone had disappeared from the urine by the second postoperative day. A single clearance determination in a man with a mixed adenocarcinoma and chorioma of the testes gave the figure of 0 23 cc.[747]

CHAPTER VIII

Excretion of Protein

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Any inference that the glomerular filtrate is absolutely protein-free is unwarranted. At a filtration rate of 130 cc/min., the excretion of 56 gm. of protein per day would require no more than 30 mg/100 cc. of protein in the glomerular filtrate if none were reabsorbed by the tubules. The excretion of urinary protein in [illegible]

[illegible] increased glomerular permeability or decreased reabsorption.* Addis[14,15] long defended the view that proteinuria reflects in some measure a decrease in the normal reabsorption by the tubules. If tubular reabsorption is accepted, attention must be given to the mechanism by which this protein is disposed of in the tubule cell, and the consequences of protein reabsorption on other tubular functions.

All other evidence indicating that the glomerular membranes act as a simple filter, it must be supposed that their permeability to protein will be conditioned in the first instance by the molecular size of the latter. This problem is complicated by the circumstance that all methods for the determination of the molecular weights of proteins yield only a statistical mean figure and afford no information on the spontaneous dissociation or accidental fragmentation of the protein into components smaller than the mean. The possible presence of a small fraction of such small molecules complicates all studies of protein excretion.

ATHROCYTOSIS

Numerous studies in a variety of species have demonstrated that the basal membrane of the proximal tubule cells is impermeable to negatively charged colloids of large molecular weight. But when such colloids gain entrance to the lumen through the open nephrostomes of nephrostomatous tubules in the Urodeles, or by intraglomerular injection, they are taken up by the cells of the proximal tubule and accumulate in visible granules.[480,792,940,1252,1905] This absorption of colloids and their concentration and retention in granular form in the apical pole of the proximal tubule is commonly known as athrocytosis (*athro* = gather; *cytosis* = cell), a term, according to Lison,[1251] which was first used by Burian and

* A history of all aspects of proteinuria is given by Jens Bing[157]

resurrected after a period of disuse by Gérard and Cordier.[782,76] The subject has been well reviewed by Rather in the *Festschrift for Thomas Addis*.[1055]

It has been said that the absorption of particulate material (melanin and cinnabar), as observed in the nephrostomatous kidney, is effected by a process of phagocytosis Lewis,[1234 1235] however, has photographed by retarded cinematography the activity of macrophages, monocytes, and epitheloid cells, and the photographs dramatically reveal that these cells, and particularly macrophages, undergo continuous changes in form which involve the formation of broad, wavy, veil-like membranous pseudopodia in the manner of a series of folds which are continuously in motion. In this motion they engulf droplets of fluid between the folds, the folds then fusing and completely enclosing the droplet. The globule thus formed is at first irregular in outline, probably because of the mechanical tensions of the engulfing folds, but it soon becomes spherical as it moves into the cell and the mechanical tensions are released The globules move toward the center of the cell, sometimes fusing with other globules, but ultimately diminishing in size as water is absorbed into the cytoplasm and presumably excreted by the cell, while any particulate contents remain as cytoplasmic inclusions Lewis has called this process of mechanically engulfing fluid 'pinocytosis' (*pino* = drink; *cytosis* = cell). The time required to engulf a droplet of fluid is only a few seconds and for the resulting globule to disappear only a few minutes, and a cell may drink several times its volume in 24 hr Pinocytosis has also been demonstrated in *in vitro* cultures of sarcoma and carcinoma cells and in normal fibroblasts.

According to Lewis, Meltzer, in 1904, suggested that 'all cells might be endowed with the submicroscopic act of "sipping" the adjacent fluid, which might indeed be a subsidiary or even an essential factor in the process of nutrition of all cells.' He suggested that this hypothetical microscopic drinking be called 'potocytosis' (*poto* = drink, *cytosis* = cell), but the term has never come into use. Lewis points out that since ruffle pseudopodia take in fluid globules down to the limits of visibility, they may also take in submicroscopic ones.

No evidence of a process similar to pinocytosis is recorded in

the renal tubules. Nevertheless, the brush border of the proximal tubule is relatively unique. A similar cytological structure occurs in the placenta, the choroid plexus of some mammalian species, and the yolk sac of the Agouti. With regard to the placenta, Wislocki and Bennett[2250] report that the outer surface of the syncytium exhibits a variable structure ranging from a brush-like border to one consisting of irregular streamers of cytoplasm. This variability they regard as normal and as attributable to instability and plasticity of the surface, by virtue of which its cytoplasm can flow and stream and hence assume various appearances. These variable manifestations bespeak an active transfer of fluid and metabolites across the surface of the trophoblast. Wislocki and Streeter[2251] interpret a variety of vacuoles in the syncytium as resulting from the pinocytosis of fluid from the intervillous space. It is therefore conceivable that the brush border of the proximal tubule participates in pinocytosis (or potocytosis), whereby colloids too large to be absorbed by membrane transfer may gain access to the cell. Lambert[1193,1196] has shown that trypan blue and India ink, the last definitely a particulate colloid, were absorbed into the proximal tubule cells in man after injection into a polycystic kidney during life. The trypan blue was taken up in the early part of the proximal tubule, the India ink more distally in this segment. If pinocytosis occurs in the human kidney, it raises a question about the disposal of inulin, creatinine, etc., which must also be simultaneously pinocytized, though the quantity of fluid thus taken in is probably very small.

In any case, the 'permeability' to colloids is at a minimum in the first portion of the proximal tubule and increases progressively distally. The larger the colloid the lower down the segment is it absorbed. Refractory colloids are generally stored in the tubule cells, although digestible proteins are ultimately disposed of.

Histological evidence involving the use of dyed proteins,* the presence of vacuoles, or the demonstration of iron pigments within the cells has demonstrated the absorption of a variety of proteins (hemoglobin, horse and dog serum albumin, egg albumin, gelatin, casein, peptone) by the proximal tubule in several species. Gran-

* Such dyed proteins are usually made by coupling with 2-naphthol-3:6 disulphonic acid to give a red compound

ules and hyalin deposits within the tubule cells associated wit proteinuria ('cloudy swelling') are believed to represent product of such absorption. It is of interest that, despite prolonged hemoglobinemia, neither hemoglobin nor hemosiderin is taken up by the Kupffer cells in the liver, by the femoral marrow, or by the spleen.[824,1550,1551,1684,1908,1909]

Oliver[1551] has given an excellent description of the cytological changes in the proximal tubules of the rat during the reabsorption of egg albumin, hemoglobin, and dyed proteins. The reabsorption process is limited to the proximal tubule and is most intense in the middle third of this segment. During the reabsorption process, droplets appear in the cytoplasm which can be identified as containing the protein involved. Concomitantly, the mitochondrial rods, as revealed by Janus green, disappear in the region of protein absorption, though they remain unchanged in other parts of the tubule. In the active region, the droplets now become Janus green positive. Egg white is itself not Janus green positive, and Oliver concludes that the droplets consist of egg white with an admixture of mitochondrial material. Damaged or immature cells do not show these cellular reactions. Hemoglobin droplets disappear fairly rapidly from the cells, while egg-white droplets require some weeks for their dissipation. A similar phenomenon occurs during the reabsorption of amino acids and, in the frog, during the excretion of neutral red. If renal cells are lacking mitochondrial substance, as regenerated cells are, no absorption by droplets occurs.

Oliver[1552] and Rather[1685] in the *Festschrift for Thomas Addis* accept Randerath's[1674] interpretation that the brilliant eosinophilic or fuchsinophilic hyalin droplets seen in the proximal epithelium in certain types of glomerulonephritis and in association with proteinuria, however produced, represent plasma proteins which are undergoing tubular reabsorption. As Oliver says, such droplets may be taken as evidence of vitality rather than of injury of the renal epithelium. Their presence may, however, be indicative of increased glomerular permeability as Randerath suggested. Rather emphasizes, however, that proteinuria is not accompanied by extensive hyalin droplet formation in rats injected with bovine albumin (where vacuolation of the proximal cells is an important feature), indicating that factors other than

an increase in the amount of protein in the tubular urine are involved.

No convincing evidence has ever been adduced for the excretion of protein by the renal tubules. Bieter [188] found that egg albumin and homologous hemoglobin, which are excreted in the urine of glomerular fishes after intravenous injection, are not excreted by the aglomerular toadfish, *nor will mercury bichloride* produce albuminuria in the latter, as it does in glomerular kidneys.

Dock [524] *has shown that, when the rabbit kidney is perfused* with ice-cold serum, a technique first used by Bickford and Winton [184] *and which presumably reduces tubular activity to a* minimum without changing glomerular permeability, the urine, *which approaches the glomerular filtrate in composition, contains* from 15 to 22 mg/100 cc. of protein. They believe that this represents *protein that is normally filtered and reabsorbed.*

Fat deposition in normal tubules shows marked species differences. This intracellular fat does not represent material reabsorbed from the tubular urine but is an accumulation resulting from local metabolic activity.[1660]

Ekehorn [593] found small quantities of protein in the capsular fluid of the frog, and suggested that a small quantity of protein was normally filtered and reabsorbed by the tubules, a suggestion which received support from the demonstration of hemoglobin in the proximal tubule cells during hemoglobinuria.[1616]

After injecting protein intravenously in cats and rabbits, or adding it to defibrinated blood during the perfusion of the isolated dog kidney, Bayliss, Kerridge, and Russell [108] found some excretion of hemoglobin (mol. wt. 68,000), egg albumin (35,000), Bence-Jones protein (35,000), and gelatin (35,000), while serum albumin (72,000), serum globulin (170,000), casein (200,000), edestin (200,000), and hemocyanin (5,000,000) were not excreted. Fixed sections of isolated kidneys that had been perfused with egg albumin for 30 min. showed a deposit of protein in the capsular space as well as in the lumen of the tubules, indicating that the protein had escaped through the glomeruli.

Bott and Richards [218] analyzed the glomerular fluid after the injection of a variety of proteins into frogs and found that, although the glomerular membranes were partially *permeable to*

proteins of the 35,200 molecular weight group, differences existed in respect to permeability toward various proteins. A purified protein derivative of tuberculin (mol. wt. 14,500) was filtered more completely than the proteins mentioned above. The authors concluded that most of the glomerular membranes permit the passage of particles of c. 50 A. Although permeability of the membrane appears to be grossly related to particle size, it is possible that other factors influence the relative permeability toward particles of approximately the same size

HEMOGLOBIN

When purified homologous hemoglobin is injected intravenously, no hemoglobinuria occurs in dogs until a plasma concentration of some 100 mg/100 cc is exceeded, above this level excretion (UV) increases in proportion to P. Lichty, Havill, and Whipple [1440] first suggested that some hemoglobin normally passes the glomerular membranes and is reabsorbed by the tubules, hemoglobinuria occurring only when the tubule cells become saturated. Monke and Yuile [1444] subsequently showed that above the 'threshold,' the hemoglobin/creatinine clearance ratio has a value ranging from 0.016 to 0.04, averaging 0.029, i.e the mean rate of filtration of hemoglobin is about 3 per cent of the filtration rate. By reference to their own and previous data, they conclude that the absence of hemoglobinuria at plasma concentrations below the critical value inducing frank excretion is attributable to tubular reabsorption by athrocytosis. They attribute to this process a maximal rate which may be designated for discussion as hemoglobin Tm, analogous to glucose Tm, etc. In this view the 'threshold' is the value of P where $C_F P = Tm$, and P will vary with C_F. An average value of the athrocytotic activity in a medium-sized dog is 2 mg/min., or 2.88 gm/day.

The uniformity of the hemoglobin/creatinine clearance ratio indicates that hemoglobinuria is not the result of transient glomerular injury induced by injection of hemoglobin, as was argued in the case of albumin by Babcock; [70] against the argument of glomerular injury, Monke and Yuile oppose the functional and histologic evidence of De Gowin, Osterhagen, and Andersch [485] and of Whipple and his coworkers. [1440, 1818] Monke and Yuile explain

the low filtration rate of hemoglobin by assuming that only 3 per cent of the 'pores' in the glomerular membrane are large enough to permit the passage of hemoglobin molecules, and consequently the glomerular filtrate carries with it only 3 per cent of the hemoglobin in the plasma. However, *the alternative, that 3 per cent of the hemoglobin in the plasma may be dissociated into molecules of a molecular weight of 17,200 (or 34,400) which readily pass through the glomerular membrane,* is not excluded by any available evidence, and, from opinions given to the writer by protein chemists, is wholly plausible.

A considerable fraction of the hemoglobin iron retained in the body accumulates temporarily in the kidneys, where it presumably represents hemoglobin derivatives (hemosiderin, etc.) formed as the tubule cells rework the protein and make the iron again available for hematopoiesis.

The repeated injection of hemoglobin in dogs leads to a decrease in the plasma concentration at which hemoglobinuria occurs, indicative of a reduction in the maximal rate of tubular reabsorption. However, in such repeatedly injected dogs, hemoglobin tagged with radioactive iron is retained in the body to a greater extent than in normal dogs, and Yuile, Steinman, Hahn, and Clark [2288] *tentatively suggest that, after repeated injection, hemoglobin is less rapidly reworked by or removed from the tubule cells.* However, a change in permeability of the glomerular membranes is not excluded and final explanation of the phenomenon must await further studies.

Lippman [1215] reports that the hemoglobin/inulin clearance ratio in rats is roughly 0.04, corresponding with the ratio 0.03 and the threshold concentration of 100 mg/100 cc. in dogs obtained by Yuile and his coworkers. Eighteen hours after the second of two intraperitoneal injections of 6 per cent bovine albumin-saline solution, the 'threshold' is lowered to less than 25 mg/100 cc. and *the slope of the line $\Delta UV:\Delta P$ is increased twofold,* from which he suggests that albumin both saturates the protein reabsorption mechanism and increases glomerular permeability to the hemoglobin.

The earlier conclusions from studies on experimental hemoglobinuria in man by Ottenberg and Fox [1560] are not wholly rec-

oncilable with these studies on dogs and rats. Ottenberg and Fox found the renal threshold to be very variable in terms of plasma concentration, but no measurements of filtration rate were made and urines were presumably collected by spontaneous voiding, under which conditions bladder and renal dead space errors as well as arterial-venous differences must have complicated the results.

Gilligan, Altschule, and Katersky[TS] administered up to 16.4 gm. of stroma-free hemoglobin solution to normal subjects, and observed hemoglobinuria in all in whom the plasma hemoglobin concentration exceeded 135 mg/100 cc. Once hemoglobinuria began, it persisted until the plasma level had decreased to 30 to 50 mg/100 cc. Small amounts of hemoglobin were excreted in the urine of patients with pre-existing proteinuria when the plasma level was elevated to only 40 to 50 mg/100 cc. Hemoglobinuria in normal subjects was accompanied by the excretion of protein other than hemoglobin, and proteinuria usually persisted for about an hour longer than hemoglobinuria. The authors believe that this proteinuria indicates a temporary increase in glomerular permeability, but blockade of normal protein reabsorption by hemoglobin was not considered. That hemoglobin (as well as methemoglobin, myohemoglobin, and metamyohemoglobin) is not toxic in normal animals with a normal filtration rate is well established (see ch XXIV)

PLASMA PROTEINS

Terry, Hawkins, Church, and Whipple[1069] have shown that when dog plasma is administered daily to dogs the plasma protein concentration rises and, at concentrations of 9.6 to 10.4 gm/100 cc., protein begins to be excreted in the urine. An interval of 4 to 26 days intervenes between the start of plasma protein injections and the appearance of proteinuria, larger doses reducing this interval. Repeated experiments in the same dog show that the critical plasma concentration leading to excretion is relatively constant. The proteinuria is physiological, in that it disappears at once when the plasma protein concentration is allowed to fall, and the kidneys show no microscopic damage. The total protein excretion may amount to 7 to 26 per cent of the protein injected. The urinary protein is composed chiefly of albumin (60 to 75 per

cent) but contains some beta and gamma globulin, alpha-1 and alpha-2 globulin being present only in traces. The authors believe that their data establish a renal threshold for plasma proteins, which by implication may be likened to the filtration-reabsorption mechanism for hemoglobin. Similarly, Waterhouse and Holler [2149] find that protein excretion is linearly related to plasma level in normal subjects when this level is increased by the injection of homologous albumin, and they accept as the most probable explanation normal filtration and limited tubular reabsorption.

When Evans blue is injected into rats, in which species there are usually traces of protein in the urine, some proximal tubule cells show the Evans blue protein complex undergoing absorption, indicative of normal tubular reabsorption.[624,785] Parenteral injection of egg albumin in the rat produces proteinuria composed of egg albumin, with no appreciable excretion of rat serum protein. But, after injection of bovine albumin, large quantities of rat serum protein are excreted in addition to bovine albumin.[1217]

The urinary protein ordinarily observed in the proteinuria of renal disease consists of a mixture of albumin and globulin, identical in their individual properties with those of plasma,[1267,1350] but differing markedly though variably in the relative proportions of albumin and globulin present.

MYOHEMOGLOBIN

Myohemoglobin has a molecular weight of 17,500, as compared with 68,800 for hemoglobin. Myohemoglobin is excreted by the dog at much lower plasma concentrations (15 to 20 mg/100 cc.) than is hemoglobin, and Yuile and Clark [2286] have found that the maximum myohemoglobin/creatinine clearance ratio in the dog averages 0.58 as compared *with 0.023 for hemoglobin. Assuming a constant, maximal* rate of tubular reabsorption, the data indicate that about 75 per cent of the myohemoglobin in the plasma passes into the glomerular filtrate, some 25 times as much as in the case of hemoglobin.

GELATIN

With reference to their use as blood substitutes, Hoffman and Kozoll [1022] studied the excretion of heavy, intermediate, and light types of gelatin

(average molecular weights 58,000, 47,000, and 37,000 respectively) after intravenous administration in man. Excretion was markedly variable even with the same lot, but a general pattern was discernible, the rate of excretion increasing from the heavy to the light type. By 72 hr., some 80 per cent of all types was excreted. The gelatin clearances decreased during the first 6 hr. after injection, presumably because of the more rapid excretion of smaller molecules. In the interval 4 to 6 hr. after injection, the gelatin/endogenous creatinine chromogen clearance ratio averaged 0.0278 ± 0.0125 for the heavy type, 0.0301 ± 0.0099 for the intermediate, and 0.0393 ± 0.0118 for the light, the difference being more marked immediately after injection. (In view of the wide dispersion in molecular weight, it would be hazardous to identify these clearance ratios with average molecular weight figures.)

The gelatin solutions did not cause diuresis, and a concentration in the urine of 15 gm/100 cc. was encountered, which could increase the viscosity enough to interfere with renal function. Plasma volume determinations showed the well-established hemodilution effect of gelatin.

These solutions of gelatin were autoclaved, which is perhaps significant, since Bridger and his coworkers [251] report that, in dogs, autoclaved gelatin-saline solutions produce no greater urine flow than the same volume of saline, whereas unautoclaved gelatin is diuretic, the excess urine flow being 169 per cent of the volume injected.

ACACIA

Goudsmit, Power, and Bollman [823] compared the effects in dogs of the constant intravenous infusion of 5 per cent glucose with a mixture of 5 per cent glucose plus 10 per cent salt-free acacia. During the infusion of the glucose-acacia mixture, the creatinine clearance remained unchanged (despite a probable large increase in plasma volume); the urea clearance fluctuated in relation to changes in urine flow; water excretion decreased as the solution of acacia was being infused but tended to return to its previous levels later in the experiments (possibly because of excitation of ADH secretion); the plasma concentration of chloride decreased, obviously largely because of the increased plasma volume, while the excretion of chloride consistently increased. No information is available on the renal clearance of acacia, but that this is very small is indicated by the persistence of acacia in the plasma for prolonged periods. Acacia as a blood substitute has been abandoned in clinical use because of adverse effects upon the liver.

OTHER PROTEINS

Heparin is excreted in the urine of anesthetized dogs after the intravenous administration of 200 units/kg. of body weight.[407] Piper[161] reports that the heparin clearance in rabbits is substantially less than the creatinine clearance. From ultrafiltration studies he finds that considerable heparin is either protein bound or too large to pass through collodion membranes, and he infers that excretion involves tubular participation. The tubular excretion of a protein-like substance is unprecedented, and the difficulties of determining the true filtrable fraction in such a case renders this inference suspect.

Insulin is not a normal constituent of rabbit's urine, but an insulin-like substance is excreted after the intravenous administration of this hormone.[267]

A protein with the chemical characteristics of a nucleoprotein is normally excreted in large amounts by male mice, females excreting much less and frequently none at all.[2212] Under uniform conditions there is a fairly constant excretion of protein in the rat, which increases on a high protein diet.[11, 21, 1457]

Virulent tubercle bacilli may be excreted by the normal kidney of the guinea pig,[2280] and *Leptospira icterohemorrhagica* have been recovered from the urine of patients with Wiel's disease.[2011] Both circumstances probably represent gross invasion of the glomerular membranes.

CHAPTER IX

The Reliability of Inulin as a Measure of Glomerular Filtration

It is convenient at this point to bring together the evidence justifying the use of inulin for the measurement of glomerular filtration. It is clear that since the absolute filtration rate in any one nephron, or in any collection of nephrons, cannot be measured directly, this evidence must consist of a comparison of simultaneous clearances of various substances under a variety of conditions, supplemented as far as possible in different species.

We may start by stating certain specifications that a substance, X, suitable for measuring glomerular filtration, must fulfil:

I. To be completely filtrable through the glomeruli, X must be completely filtrable from plasma through artificial membranes impermeable to plasma proteins but permeable to smaller molecules.

II. As presumptive evidence against tubular excretion, X should not be excreted by the aglomerular fish kidney.

III. a. The rate of excretion (U_XV) of X must increase over wide limits in simple, direct proportion to the plasma concentration (P_X); i.e. the clearance, U_XV/P_X, must be independent of plasma concentration. Although not without the possibility of exceptions (note xylose, galactose, and urea) this circumstance in large measure excludes the probability of tubular excretion or reabsorption, both of which processes are limited by maximal rates

of tubular transfer which tend to destroy the relation, $U_XV \simeq P_X$.

b. Where III. a cannot be demonstrated because of inconstancy of the filtration rate itself, it is of equal force to show that the clearance of X is constant, relative to the clearance of some indifferent substance, at various plasma levels of X.

IV. Where the simultaneous clearances of X and one or more other substances are identical under a wide variety of conditions (plasma concentration, urine flow, etc.), this may be taken as evidence that both substances are excreted without the specific limitations inherent in tubular reabsorption or excretion.

V. Where one substance, A, is believed on independent evidence to be reabsorbed by the tubules, or another substance, B, is believed to be excreted by the tubules, the clearances of A and B should, if they are completely filtrable from plasma, approach the clearance of X as a limiting asymptote when the plasma concentrations of A or B, respectively, are raised to high values. If *A or B is not completely filtrable, the asymptote should be* FWC_X, where FW is the percentage of A or B filtrable from the plasma at high plasma concentrations.

VI. a. After adequate doses of phlorizin, the excretion of glucose increases in simple proportion to the concentration of glucose in the plasma, a circumstance warranting the conclusion that phlorizin in adequate doses completely blocks reabsorption by the tubules. *In this view, the clearance of X in the phlorizinized animal* should be equal to the glucose clearance. (This does not preclude the possibility that phlorizin may block the tubular excretion or reabsorption of X itself.)

b. Independent evidence indicates that phlorizin blocks the tubular excretion of many substances. Assuming that, after adequate doses of phlorizin, tubular excretion is completely blocked, then in the phlorizinized animal the clearance of such a substance should be reduced to that of X, or to C_XFW if the substance is not completely filtrable.

VII. Where two substances compete for a common mechanism of tubular reabsorption or excretion, saturation of the tubular mechanism by the stronger should cause the clearance of the weaker to approach the clearance of X or to approach C_XFW if the obstructed substance is not completely filtrable.

The following paragraphs detail the behavior of inulin in the foregoing respects:

1. Inulin is not bound by plasma proteins.[977,1868]

2. Inulin is not excreted by the aglomerular kidney of the toadfish,[1720,1846] goosefish,[1545] or batfish;[1928] in the last instance the urine was shown to contain less than 5 mg./100 cc. when the plasma had contained some 1600 mg./100 cc. for many hours.

3. a. The rate of excretion of inulin, UV, is proportional to P in the dog between 53 and 565 mg./100 cc.,[1846] and in man between 50 and 400 mg. per cent[1868] and between 5 and 90 mg./100 cc[1449]

b The creatinine/inulin clearance ratio (1.0) is independent of the plasma level of inulin in the dog.[1720,1846]

4. a. The simultaneous inulin and creatinine clearances are identical in the frog (0 996 ± 0 064),[674] turtle,[698] dog (0.99 ± 0.03),[1720,1721,1846,1849,2093] rabbit (0 99 ± 0 04),[1090] sheep (1.03),[1861] and seal (0.98).[1927] In the dog the creatinine clearance is independent of the plasma creatinine concentration over wide ranges,[1846] and this is true of the creatinine/inulin clearance ratio in the rabbit[1090] and frog.[674] (This identity does not obtain in the dogfish, teleost, chicken, ape, or man; in all except the ape, independent evidence for the tubular excretion of creatinine has been adduced.)

b. The simultaneous inulin and ferrocyanide clearances are identical in the dog.[2093] (Lack of identity between these clearances in man is attributed to tubular reabsorption of ferrocyanide,[1451] but this point has been questioned in chapter VII.)

The simultaneous inulin and allantoin clearances are identical in man,[710] and the allantoin and inulin clearances are identical in the dog and rat[707]

The sorbitol, mannitol, dulcitol, and sorbitan clearances were said to be identical, within the limit of experimental error, with the simultaneous creatinine and inulin clearances in the dog, and with the simultaneous inulin clearance in man,[1848] the hexitols being determined by yeasting and periodate oxidation. When the chromotropic acid method is used for the analysis of mannitol, the mannitol/creatinine clearance ratio in the dog and the mannitol/inulin clearance ratio in man average about 0.90. The identity of these clearances may therefore be held to be open to ques-

tion until analytical difficulties are resolved (see mannitol, ch. VII).

(The thiosulphate clearance has been reported to be identical with the creatinine clearance in the dog[781] and the inulin clearance in man,[1514] an apparent identity that has been confirmed by several investigators. However, in normal cats and in pregnant dogs and women, and after the administration of carinamide, this identity is not maintained, and the significance of the identity under other conditions is open to question.)

5. a. Tubular excretion. Elevation of the plasma level of various solutes believed on independent evidence to be excreted by the tubules depresses the inulin (or, in the dog, creatinine) clearance ratio with respect to these solutes toward 1.0 where the solute is wholly ultrafiltrable or toward $C_X FW$ where the solute is bound to plasma protein: *creatinine:* dogfish,[1865] teleost,[1626] chicken,[1833] and chimpanzee;[1936] *creatine:* dogfish[1929] and grouper;[1626] *phenol red:* dogfish,[1945] dog,[1847] and man;[800,1938] *uric acid:* chicken;[1866] *iopax* and *neoiopax:* man;[1919] *diodrast* and *hippuran;*[1938] *p-aminohippuric acid.*[362]

b. Tubular reabsorption. Elevation of the plasma level of various solutes believed on independent evidence to be reabsorbed by the tubules raises the inulin (or, in the dog, creatinine) clearance ratio with respect to these solutes toward 1.0: *glucose:* dog[1884] and man;[1931] *creatine:* dog and man;[1621] *vitamin C:* dog,[1877] and man;[1670] *pantothenic acid;*[2275] *phosphate;*[1636] *amino acids;*[1626,1611] *sulphate:* dog;[1273] *uric acid:* man (Berliner, pers. com.). Although these (5. a and b) results are more qualitative than quantitative, the fact that in most instances a reproducible maximal rate of tubular reabsorption or excretion can be demonstrated by using the inulin (or, in the dog, creatinine) clearance as the measure of filtration is supportive evidence for the premise. Moreover, in a few cases where Tm is small relative to physiologically possible loads, the clearance ratio at elevated plasma levels may closely approach 1.0, as in the case of creatinine in man (1.1) and chimpanzee (1.0), of phosphate in the dog (0.9+), and of vitamin C in the dog (0.95+) and man (0.90+).

Govaerts, Lambert, Lebrun, and de Heinzelin de Braucourt[828] have shown that the filtration rate calculated from the ratio

$\Delta U_G V/\Delta P_G$ at values of P_G above that required to cause frank glucuresis checks with the simultaneous thiosulphate clearance in man. Inasmuch as the thiosulphate clearance has been equated

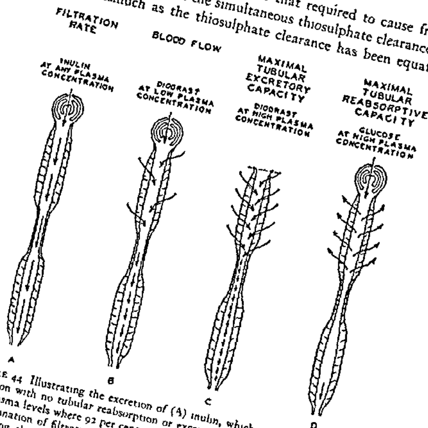


FIGURE 44 Illustrating the excretion of (A) inulin, which is excreted solely by filtration with no tubular reabsorption or excretion, (B) diodrast (or PAH) at low plasma levels where 92 per cent is removed from the renal arterial blood by a combination of filtration and tubular excretion, thus affording a method for measuring the renal blood flow, (C) maximal tubular excretory capacity for diodrast (Tm_D) or PAH (Tm_{PAH}) after correction for the quantity filtered, affording a specific measure of the quantity of tubular excretory tissue; (D) maximal tubular reabsorptive capacity for glucose, affording a specific measure of tubular reabsorptive activity

with the inulin clearance in man, this correspondence may be considered significant, but since the equation between the thiosulphate and inulin clearances has been questioned as fortuitous, this evidence must be considered to be of secondary weight. The

principle, however, is sound, and applicable to any substance if a constant rate of reabsorption or excretion is accepted.

6. a. Administration of phlorizin raises the glucose/inulin or creatinine clearance ratio from 0.0 to 1.00 in the dogfish,[1845] to 1.0 in the teleost,[1626] to 1.01 in the dog,[1846,1847,1936] to 0.96 in the chicken,[1628,1855] *to 0.93 in the chimpanzee,*[1938] *and (in the largest* dose given, 100 mg/kg.) to 0.91 in man. It raises the xylose/inulin or creatinine clearance ratio from 0.78 to 1.0 in the dogfish,[1845] from 0.73 to 0.97 in the dog,[1620,1626] and from 0.78 to 0.90 in man (100 mg/kg.). * [1868]

b. Administration of phlorizin lowers the creatinine/inulin ratio in the chicken from 1.59 to 0.98,[1855] in the chimpanzee from 1.27 to 1.05,[1938] and in man from 1.39 to 1.00.[1848]

7. *Glucose and xylose are reabsorbed by a common mechanism,* and saturation of the tubules by glucose raises the xylose/inulin clearance ratio in the dog from 0.78 to 1.0 [1852] and from 0.80 to 0.96 or higher in the frog.[676] *Amino acids and creatine are re-*absorbed by a common mechanism, and saturation of the tubules by glycine or alanine raises the creatine/creatinine ratio to 1.0 in the dog.

Supplementing the foregoing clearance comparisons are the experiments of Richards, Bott, and Westfall,[1711] who have shown that when inulin is perfused through the renal-portal vessels of the frog's kidney none gains access to the lumen unless the tubules are injured, thus excluding tubular excretion in this species. When inulin, along with phenol red, diodrast, or hippuran, is perfused through the dog or rabbit kidney at a pressure below that necessary to effect filtration, phenol red, diodrast, and hippuran accumulate in the tubules and are washed out when filtration is re-established by perfusion at a higher pressure, but so little inulin is present in this urine that the tubular excretion of this substance may be excluded.

is.

* For sucrose/xylose and glucose/sucrose ratios in normal and phlorizinized animals see Smith,[1915,1918] and for other comparisons of clearance ratios see [404,1781, 2107 2208].

But the total evidence can best be explained by the interpretati that the inulin clearance in all species is identical with the filtr tion rate.

This evidence can be briefly summarized as follows:

Inulin is completely filtrable from the plasma. It is not ex- creted by the aglomerular fish kidney. In the dog and man the

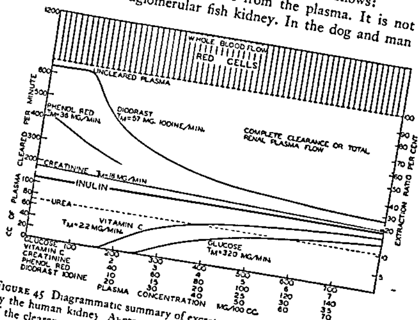


FIGURE 45 Diagrammatic summary of excretion of various types of compounds by the human kidney Average normal Tm values are used in the calculation of the clearances at various plasma levels

rate of excretion (*UV*) increases in direct proportion to *P*, indicating absence of tubular participation either in excretion or reabsorption.

In normal man, the simultaneous inulin, allantoin, sorbitol, dulcitol, mannitol and sorbitan (and, in the dog, creatinine) clearances are identical, presumptive evidence that they are at the level of the glomerular clearance.

Elevation of the plasma concentration of substances for which there is independent evidence of tubular excretion or reabsorption (i.e. variability of clearance with P or of substances competing for tubular transport) causes the clearances of these substances

to converge toward the inulin clearance. Thus, at physiologically tolerable plasma concentrations, the creatine, phosphate, and vitamin C clearances are only slightly less than the inulin clearance in man, while saturation of the tubules with glucose brings the xylose clearance up to the creatinine clearance, and saturation with glycine or alanine brings the creatine clearance up to the *creatinine clearance in the dog.*

In the phlorizinized dog, the glucose, xylose, and sucrose clearances are identical with the creatinine clearance; with somewhat smaller doses of phlorizin, these clearances are only slightly below the inulin clearance in man, while the inulin and creatinine clearances are identical.

In closing this chapter, it is convenient to summarize possible modes of excretion (exclusive of the tubular synthesis of ammonia, etc.), a summary that can be presented very simply in diagrammatic form (fig. 44).

Another simple diagram (fig. 45) will serve to show the rate of renal clearance of a variety of substances, in relation to the inulin clearance, at various plasma concentrations of these substances, where their excretion is governed by a critical constant (Tm) in tubular transport. The Tm values used in calculating the clearances in figure 45 are taken from the studies in preceding chapters. In the case of urea, which is reabsorbed by passive diffusion, the clearance at a fixed filtration rate and urine flow is essentially independent *of plasma concentration.*

Part II

CHAPTER X

The Antidiuretic Hormone and the Excretion of Water

GENERAL CONSIDERATIONS

It has been known for three decades that clinical or experimental lesions involving the posterior pituitary gland, or certain tracts in the hypothalamus related to this gland, may result in a greatly increased urine flow (polyuria) and an insatiable thirst (polydipsia), this syndrome being known as diabetes insipidus. It is clearly established that in experimental diabetes insipidus polyuria is primary and polydipsia secondary,* and that the polyuria is a result of a deficient secretion of the antidiuretic hormone (ADH), so called because, when administered to normal animals, it prevents the [illegible] of water. [illegible] 20 liters/ [illegible] any remedy other than greatly increased water ingestion the condition may persist for many years.

PASSIVE AND ACTIVE WATER REABSORPTION IN THE TUBULES

In the current view, the reabsorption of water by the renal tubules involves at least two more or less independent processes:

* The French school of clinical neurologists maintains that, *in some individuals* with apparent diabetes *insipidus*, polydipsia is primary and is related to a lesion in the hypothalamus [illegible]

† Figures of 40 liters/day are quoted by Fisher *et al* [illegible] This figure is theoretically possible with a filtration rate of 180 cc/min., but such high figures should be checked under supervision.

(1) passive water reabsorption in the proximal tubule and thin segment (proximal system), and, under appropriate circumstances, in the distal tubule; and (2) active water reabsorption that is presumably confined to the distal system, i.e. in the distal tubule and possibly in the collecting ducts also. So far as is known, only active water reabsorption is under rapidly variable hormonal control.

PASSIVE WATER REABSORPTION

The evidence for the belief that water reabsorption involves these two processes is based in part on the urea/inulin clearance ratio at varying urine flows (ch. IV, fig. 11) and in part on the fact that the minimal inulin U/P ratio in normal dogs and man during maximal water diuresis ranges from 6 to 10,[261,1840] and from 8 to 10 in dogs with experimental diabetes insipidus [910,1861] and in man with severe clinical diabetes insipidus.[673,2234]

Ludemann, Raisz, and Wirz (pers. com.) have studied the minimal creatinine U/P ratio in dogs during maximal water diuresis (water loads of 150 to 250 cc/kg. in 2 doses 30 min apart) at varying levels of the filtration rate, achieved by maintaining the animals on low protein (cracker meal, lard, and sugar), moderate protein (standard dog chow), and high protein (fresh horse meat) diets. On the meat diet, the postprandial clearance ranged from 35 to 60 per cent above the postabsorptive figures observed on the other two diets. Observations were made both postabsorptively and postprandially. Minimal creatinine U/P ratios were attained 1 to 2 hr. after the first dose of water and were usually maintained for several 10 min. collection periods. The minimal U/P ratio varied from 7.0 to 9.8 at the lower filtration rate, and from 5.4 to 8.4 at the higher rate. The results were not influenced by the sequence in which the diets were fed It has not yet been determined what effect the excretion of urea and other osmotically active substances, apart from electrolytes, may have in the foregoing experiments on the delivery of water to the distal system, but it appears that the distal fraction will tend to increase with increasing filtration rate.

For discussion, the average figure of 8 will be used. This means that during maximal water diuresis the glomerular filtrate has been concentrated about eightfold, or that some seven-eighths of the water originally present in the filtrate has been reabsorbed. At a filtration rate of 130 cc/min., this represents the reabsorption

of 114 cc/min., leaving 16 cc/min., more or less, as the maximal diuretic urine flow.

It is believed that this seven-eighths (in round numbers 85 per cent) of the glomerular filtrate is reabsorbed in the proximal tubule and thin segment of Henle's loop by a passive process, concomitantly with or in consequence of the reabsorption by the proximal tubule of electrolytes, glucose, etc.* (see fig. 60, p. 327).[1926] That this proximal reabsorption of water is a passive process is indicated by several lines of evidence which will be presented later (ch. XI). Passive diffusion across the tubule presumably occurs *pari passu* with the reabsorption of sodium, chloride, bicarbonate, glucose, etc., to maintain an osmotic U/P ratio close to 1.0. The proximal reabsorption of sodium and glucose are certainly active operations, and this reabsorption of osmotically active constituents will tend to leave the tubular urine hypotonic to the blood. It may be presumed that, in so far as time permits, water diffuses from this hypotonic urine back into the blood in consequence of the resulting difference in osmotic pressure. Further diffusion occurs in the thin segment of the loop of Henle, the function of which is now considered to be the promotion of osmotic equilibrium between the tubular urine and the blood before the urine is delivered to the distal tubule. Because water reabsorption in the proximal tubule and thin segment is physiologically uncontrolled, as far as the maintenance of water equilibrium is concerned, the writer [1926] previously called it 'obligatory water reabsorption.'

This passive reabsorption of water can be impeded and the minimal U/P ratio decreased by loading the urine with unreabsorbed, osmotically active substances such as glucose, mannitol, urea, etc. Thus, during glucose, sulphate, mannitol, or urea diuresis, creatinine U/P ratios substantially less than 2.0 have been obtained

pig) Each unit length of the proximal tubule appears to reabsorb a constant percentage of the glomerular filtrate rather than a constant absolute amount. They estimate that, by the end of the proximal tubule (exclusive of the thin limb), perhaps 80 per cent of the water has been reabsorbed, yielding a U/P ratio of 100/(100 − 80), or 5.0

in dogs and rabbits.[1486,1797,1883,2178] Inulin U/P ratios as low as 35 have been recorded in man during severe glucose diuresis (i.e. urine flows as high as 41 cc/min.),* [1931,1939] while an inulin U/P ratio of nearly 1.0 has been obtained in the chicken.[2161]

ACTIVE WATER REABSORPTION

Supplementary to obligatory water reabsorption is an active reabsorptive process which is promoted by ADH; it is by variations in this moiety (i.e. about 15 per cent of the glomerular filtrate, or c.16 to 20 cc/min. in man) that the urine flow is adjusted to meet the normal water requirements of the body. This active process the writer designated as 'facultative reabsorption.' The evidence favors the belief that facultative reabsorption is confined to the distal portions of the nephron, possibly to the distal segment, though there is reason to believe that the collecting ducts may be involved. When facultative reabsorption is in abeyance, the urine flow is large and the urine osmotically very dilute because of the reabsorption of sodium chloride in the distal tubule; when facultative reabsorption is maximal, the urine flow is small and the urine is concentrated.

That the renal tubules in the dog, in the entire (or almost entire) absence of ADH, are capable of elaborating a hypertonic urine during water deprivation has been shown by Fisher, Ingram, and Ranson,[686] who were able to deprive diabetes insipidus cats of water for a period as long as 8 days. The specific gravity of the urine rose to 1.044 to 0,050. White and Heinbecker[2198] obtained similar results with diabetes insipidus dogs. Shannon[1881] obtained osmotic U/P ratios of 1.30, 1.63, and 1.32 in 3 dogs deprived of water for 24 hr., and he suggested that dehydration, presumably through an increase in the osmotic pressure of the plasma, imposes upon the distal system the physiological conditions favoring the formation of a concentrated urine, and that ADH serves to effect a more efficient conservation of water by reinforcing this intrinsic tubular process. However, the maximal recorded osmotic pressure of the urine of a diabetes insipidus dog

* Extreme osmotic diuresis if maintained is dangerous since it may lead to sudden and critical dehydration.

is $\Delta = -1.01°$ C., whereas this value may reach $-3.0°$ C. in normal animals (plasma $\Delta = c.0.60°$ C.), and the ability of the kidney to concentrate in the absence of ADH manifests itself only under extreme stress, with contraction of both extracellular and intracellular fluid spaces, and under conditions that are not compatible with life.[494]

THE SITE OF WATER REABSORPTION

Sections of kidneys fixed during the excretion of precipitable indicators, such as ferrocyanide, hemoglobin, uric acid, etc., reveal a progressive increase in density of indicator as the urine passes down the proximal tubule, the thin limb, and the distal tubule, culminating in the collecting ducts.[120, 654, 572, 573, 764, 765, 771, 1032, 2118] In many clinical disturbances, plasma proteins or hemoglobin escape through the glomeruli in sufficient concentration to precipitate in the urine with the formation of casts. Such coagula are not formed uniformly in all parts of the nephron, but occur particularly in the distal convolution and collecting ducts, less frequently in the ascending limb, and rarely in the thin limb and proximal tubule.[1550] These observations are consonant with the view that water reabsorption occurs throughout the length of the nephron, but they do not supply any quantitative information. It is reasonable to expect that osmotic concentration would be carried out as far down the tubule as possible, after other major reabsorptive processes had been completed

Peter [1595] suggested that the length of the thin segment in the kidneys of various mammals correlated with the maximal concentration of the urine, but the data were scarcely adequate to warrant a firm statement on this matter. Crane [445] noted that hypertonic urine is formed only in the mammals and birds in which the thin segment is present (this segment is absent in the reptiles and all lower forms, and it is present in only a small fraction of the bird's nephrons); Burgess, Harvey, and Marshall [294] pointed out that it is only in birds and mammals that ADH increases the tubular reabsorption of water. This led to the view that the urine was concentrated chiefly in the thin segment, but the thinness of the tubular epithelium in this segment has always

been a difficulty in this interpretation,* and more recent work indicates that the function of the thin segment is to promote osmotic equilibration before the urine is delivered to the distal segment where the final operations on water and sodium are performed. We must here leave open the question whether or not the collecting ducts participate in the active adsorption of water and the formation of a hypertonic urine, and no distinction can be made between the ascending limb and the convoluted portion of the distal tubule, though Walker, Bott, Oliver, and MacDowell [1131] indicate that active reabsorption may occur only in the late distal tubule and the postdistal collecting ducts.

ROLE OF THE NEUROHYPOPHYSIS AND THE ANTIDIURETIC HORMONE

DIABETES INSIPIDUS

The relationship of the pituitary gland and hypothalamus to clinical and experimental diabetes insipidus has been the subject of numerous investigations, and indeed more papers have been published in this field than in any other in renal physiology. The subject got off to a bad start and has been marked by many contradictory results and theories—Fisher, Ingram, and Ranson [666] remark that the history of diabetes insipidus reads like a comedy of experimental errors, and the recent report of Bykow [295] that neither conditioned water diuresis nor conditioned inhibition of diuresis is abolished unless both hypophysectomy and renal denervation are carried out reveals that the problem is not yet free of the possibility of error It is beyond the province of this chapter to discuss the full history of this problem, and for detailed descriptions of investigations, up to 1938, dealing with experimental and clinical lesions of the pituitary gland and related areas, reference may be made to Fisher, Ingram, and Ranson's monograph.[658]

THE ANATOMY OF THE HYPOPHYSIS AND RELATED HYPOTHALAMIC AREAS

The following outline, drawn chiefly from the description given by Fisher and his colleagues and based upon their own extensive

* That thin epithelium can do osmotic work is attested by the respiratory epithelium covering the lamellae in the gills of fish [illegible]

experiments on cats and upon work of their predecessors, will afford a summary from which subsequent investigations may be conveniently described. The description is in agreement on all major points with the views of Verney, Pickford, Heller, Richter, White, and others who have worked extensively in this field.

The hypophysis of the cat and, with few exceptions, of other mammals consists of a glandular division, the adenohypophysis, and a neural division, the neurohypophysis, each separable into the following parts (fig 46):[1111]

Adenohypophysis (glandular division)
1. Pars distalis (anterior lobe)
2. Pars tuberalis
3. Pars intermedia

Neurohypophysis (neural division)
1. Infundibular process (neural lobe; pars nervosa) } Posterior lobe *
2. Infundibular stem } Infundibulum (neural stalk)
3. Median eminence or tubercinerum } Infundibulum (neural stalk)

The median eminence has the same histological structure as the infundibular process and the infundibular stem and is therefore included as part of the neurohypophysis, rather than of the hypothalamus with which it is anatomically associated. In the cat, all three parts of the neurohypophysis contain extensions of the III ventricle (central cavity) but this condition exists only in the *Felidae*. In other mammals, the infundibular stem and infundibular process are solid and contain no extension of the ventricular cavity.

Unmyelinated nerve fibers enter the infundibular process from the supraoptic nuclei, the ventral paraventricular nuclei,[1117] and,

* Fisher, Ingram, and Ranson discard the term 'posterior' lobe since, as generally used, it refers to the infundibular process and the investing pars intermedia, and thus includes parts of both the adenohypophysis and the neurohypophysis The term is also open to criticism because it makes no provision for the median eminence and the infundibular stem, which appear to be identical in structure and are probably identical in function with the infundibular process. Thus the term *neurohypophysis* will be used in this volume, as by Fisher, Ingram, and Ranson, to indicate the structurally and presumably functionally identical infundibular process, infundibular stem and median eminence.

according to Fisher *et al.*,[656] the ventro medial nucleus, and perhaps from the anterior hypothalamic nucleus and the dorsal paraventricular nucleus, all passing to the infundibular process by way of the median eminence and constituting the *supraoptico-hypophysial tract.* The name is warranted since the majority of these fibers undoubtedly come from the supraoptic nucleus.*

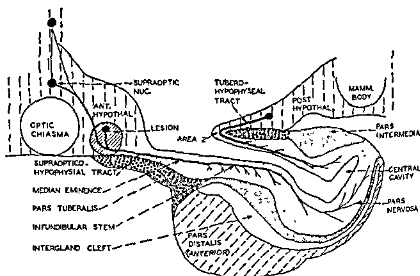


FIGURE 46 Diagram of a mid-sagittal section through the hypothalamus and hypophysis of the c [illegible] tubero-hypophysial tracts. [illegible] cal lesion designed [illegible] son [656])

EXPERIMENTAL DIABETES INSIPIDUS

The only methods of producing diabetes insipidus are to interrupt bilaterally the fibers originating in the supraoptic (and perhaps in the other) nuclei and entering the neural division of the hypophysis; or to excise the infundibular stem and median eminence as well as the infundibular process; or to remove or section the stem and eminence, in which case the infundibular process undergoes 'atrophy.' † Failure to accomplish complete removal of the

* According to Heinbecker and White,[848] the neurohypophysis is innervated only by fibers from the supraoptic and paraventricular nuclei

† The 'atrophic' changes are not too well defined, as pointed out by *Fisher et al.*

stem and eminence or to effect complete denervation is held to be responsible for the negative results reported by many investigators who have failed to obtain diabetes insipidus by 'posterior lobectomy.' O'Connor does not believe that the number of cells in the supraoptic nuclei can be related to the severity of polyuria,

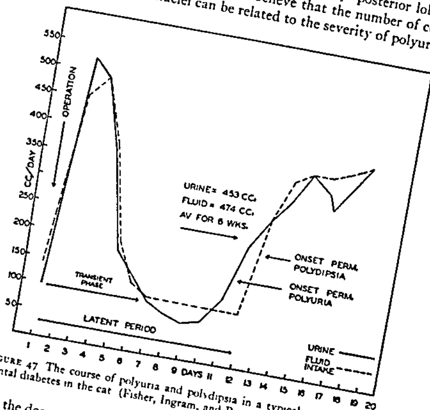


FIGURE 47 The course of polyuria and polydipsia in a typical case of experimental diabetes in the cat (Fisher, Ingram, and Ranson)

but the dogs upon which he bases this opinion showed only a very slight polyuria O'Connor and Verney had earlier expressed the view that 5 per cent of residual functional tissue suffices to constrain the urine flow within normal limits, and others believe that some 3 per cent is incompatible with maximal polyuria. Destruction of the posterior hypothalamus and of the tubero-hypophysial tract which arises from it does not cause any apparent disturbance in water balance. Lesions producing diabetes

insipidus produce 'degenerative' changes in the cells of the neurohypophysis and disappearance of nearly all extractable antidiuretic activity.[655, 767, 770, 1605, 1683, 2156]

The typical course of diabetes insipidus in a cat in which the supraopticohypophysial tract had been destroyed bilaterally by electrolytic lesions is shown in figure 47. The urine flow increased from 100 to 500 cc/day by the second day after the operation. From this peak it gradually decreased and at the end of the sixth postoperative day had returned to normal, remaining at normal levels until the eleventh postoperative day when it began to increase again. After the fifteenth day it leveled off at a value around 400 cc/day, this polyuria being maintained for 71 days of observation. Fisher, Ingram, and Ranson refer to the first phase of polyuria as the 'transient phase'; the persistent polyuria that becomes evident in the majority of cases from the tenth to the fourteenth postoperative day they designate the 'permanent phase'; and by 'normal interphase' they designate the period of normal fluid exchange that occurs between the transient and permanent phases. The entire period between the time of operation and the day of onset of the permanent phase they call the 'latent period.'

Within 24 hr. after operation in the dog, the water exchange increases from a few hundred cc/day up to 3 to 10 liters, and remains at a high level for 5 to 11 days. The interphase, during which water exchange occurs at a normal level, lasts 3 to 6 days. The permanent phase develops between the tenth and fifteenth day, when the water exchange may again reach 10 liters/day. Dogs with permanent polyuria have survived for over 4 years without recession in urine flow.[494]

Heinbecker and White [948] attribute the transient phase to traumatic injury of the secretory tissue, after subsidence of the effects of trauma there follows the normal interphase during which the denervated neurohypophysis continues to secrete hormone, and this is succeeded by permanent polyuria when cell degeneration, resulting from loss of trophic nerve influences, leads to complete failure of secretion. They believe that complete removal of all secretory tissue invariably results in the immediate development of permanent polyuria, but others have not observed this phenomenon.

Since the quantity of total solids excreted per day remains fairly constant, the specific gravity of the urine varies inversely *with the urine volume, falling to 1.003 to 1.006* during polyuria, and this value may be used as an adjunct to the measurement of urine output in following the course of polyuria. Hare and his co-workers [917] have used the U/P ratio of creatinine to judge the polyuria, for in the moderately hydrated, fully diabetic animal this decreases to 10 or below. All of these criteria fall short of reliability because they are all subject to glomerular-tubular balance.

Quantitatively, the phenomena described above show considerable variation in individual animals. The transient phase may be absent, and it does not appear later *than the second* postoperative day; it *may* last *from 1 to 11 days and (rarely) may* merge with the permanent phase, thus abolishing the normal interphase.[2211] The maximal urine output in the transient phase usually *occurs on the first or second postoperative day. The latent period ranges from 6 to 18 days, with a mode of 11 days.**

It is well demonstrated that polyuria is primary and polydipsia secondary in both the transient and permanent phases,[1774] and, since in all *species* both the *transient and permanent* polyuria can be controlled by the administration of ADH, the conclusion is warranted that the polyuria of experimental diabetes insipidus is attributable to a deficiency of this *hormone* This is not always *true of polyuria as observed in man (vide infra).*

Richter [1726] has indicated that the voluntary water intake in normal animals and humans is a function of surface area rather than body weight, and hence probably a function of metabolic rate. The figures cited range from 1050 to 1283 (average 1142) cc/sq. m per day in rats, cats,† dogs, monkeys, and humans He believed that the maximal

* In 2 cases of diabetes insipidus of traumatic origin in man, polyuria became manifest 8 and 12 days, respectively, after injury.[888]

[illegible]

diabetes insipidus cats but has no action on the 24 hr. urine volume in normal animals, presumably because of the oliguric nature of the urine.[864] It is well known that both cats and dogs, if maintained on a moist diet, can be habituated to a very small water consumption.

voluntary intake in animals with diabetes insipidus is related more closely to body weight than surface area; approximately 1000 cc/kg. per day for rats and humans, and slightly lower in cats, dogs, and monkeys, owing, he suggests, to the fact that maximal diuresis has rarely been obtained in these species because of incomplete destruction of neurohypophysial tissue. Richter's estimates, however, appear to be excessive. In theory, a man with a filtration rate of 130 cc/min. (187 liters/day), with a minimal U/P ratio of 8, would excrete 23 liters/day, or some 330 cc/kg. If we take the average filtration rate per kg of body weight in the dog as 4.3, in the cat as 3.2,* and in the rat as 6.0 cc/kg. per min., the maximal urine flow at a U/P ratio of 8 would be 774, 560, and 1080 cc/kg. per day. Variations from the mean figures for the filtration rate might encompass Richter's estimates, except in man. It is to be noted that, in the only case of diabetes insipidus in man on which information is available, the total hormone content of the posterior lobe was less than 1 per cent of normal.[989]

It is stated that the diuretic response to water in experimental diabetes is blunted and frequently imperceptible.[486,1616,1861,2191,2198] This problem is complicated by the role of the anterior pituitary gland. If this gland is intact, diabetes insipidus dogs excrete in 3 *hr.* nearly as large a *fraction* of administered water as do normal animals. Pickford and Ritchie[1616] in some instances obtained a diuretic response slightly greater than normal It must be recognized that the mechanism of water diuresis in a completely diabetic animal is different than in the normal in that it involves readjustment of glomerular activity and possibly other factors rather than changes in facultative water reabsorption. If the anterior pituitary is removed, the diuretic response is greatly blunted for reasons having nothing to do with diabetes insipidus *per se*.

The oral ingestion of saline aggravates the polyuria, and the fluid exchange is to a large extent dependent upon the sodium chloride intake, *especially if this is above normal.*[1861,1862 2027,2028,2033,2246] This effect is in part attributable to the fact that a high sodium chloride intake transiently increases the filtration rate, especially in the dog, but it also *involves the fact that the load of salt and water delivered to the* distal system is substantially increased, possibly independently of the filtration rate, and makes more water available for excretion. These same factors underlie the increase in polyuria associated with a high *protein* diet and increased excretion of urea and other metabolites.

* Calculated from Wirz[2249] as 50 cc/min. per sq m. times 0 2 sq. m/3 1 kg for an average cat.

Although some animals suffer severe dehydration and die in the course of days or weeks when the fluid allowance is reduced to the normal level, many survive for considerable periods. Such surviving animals tend to remain in a chronic state of water deficit which is made up when abundant water is given.[657, 2025] Dogs with permanent polyuria may show temporary, inexplicable periods of normal rates of urine output,[2198] and polyuria decreases in cats when fasting, independently of continued moderate salt intake.[2246] Polyuria persists, however, if the urine flow is compared with that of fasting animals under the same conditions, where the urine flow is normally very low. The effect of fasting on polyuria is in part attributable to the reduction in the excretion of nitrogenous compounds which, as noted above, increase the load by water delivered distally.* Polyuria can be markedly reduced by keeping both the nitrogenous and salt intake low.[2243]

The urge to drink in the normal and diabetes insipidus dog is not dependent on the integrity of the olfactory, gustatory, or trigeminal nerves.[118] The vagus is reported to have central secretory connections with the hypothalamico-hypophysial system, the evidence is suggestive though less certain for the olfactory, optic, lingual, vestibular, glosso-pharyngeal, and hypoglossal nerves, and negative for the trigeminal, cochlear, motor facial, spinal, and phrenic nerves.[344, 345, 1048]

Animals with diabetes insipidus, unless dehydrated, have normal concentrations of serum sodium, potassium, and chloride, and these are not affected by injections of ADH;[2244] but water restriction or sodium chloride ingestion produces negative water balance, hemoconcentration, elevation of plasma sodium and chloride levels, and loss of potassium. These changes diminish with time through unexplained adaptations.[350]

PHYSIOLOGICAL PROPERTIES OF THE ANTIDIURETIC HORMONE

THE IDENTITY OF THE POSTERIOR PITUITARY HORMONES

The known hormones extractable from the posterior pituitary are:

✓ 1. *Antidiuretic-vasopressor principle* (ADH, pitressin, vasopressin), characterized by (a) antidiuretic action and (b) pressor action when administered intravenously in anesthetized animals. ADH also causes contraction of other smooth muscles (gut) as well as the blood vessels. It constricts the coronary vessels[657] and thereby causes dilatation of the heart, a phenomenon which may contribute to the 'pressor' action.

* Possible reduction in filtration rate on a low protein diet or, in [illegible] animals should not be overlooked

2. *Oxytocic principle* (pitocin, oxytocin) characterized by ca ity to stimulate the uterus, this being the only smooth muscle u which it acts.

3. *Amphibian water balance principle*, characterized by its pacity to promote water absorption through the skin. It occurs the neurohypophysis of all vertebrate classes examined, but act so far as is known, only in the Amphibia.

4. *Melanophore principle*, characterized by its capacity to caus contraction of melanophores in cold-blooded animals generally.

The antidiuretic-vasopressor, oxytocic, and amphibian water balance principles are derived from the neurohypophysis, the melanophore principle from the pars intermedia.[656]

The amphibian water balance principle is contained in the pitocin fraction but it is probably not identical with pitocin. Heller[956] has reviewed the distribution and action of this principle.

The melanophore principle is apparently an independent entity. It has no antidiuretic activity[219, 689]

All investigators are agreed that in commercial extracts pitressin and pitocin are independent entities,* although perfect separation has proved to be difficult, the best preparations containing about 10 per cent of the other activity.[841, 974, 1055, 1994] Both principles are amphoteric; pitressin has an isoelectric point at about pH 10.85, pitocin at about pH 8.5.[893, 1062] The latter has no pressor action.

Pitressin (ADH) occurs in the pituitary of all classes of vertebrates,[956] though the pituitaries of mammals contain 8 or more times as much as in any other Class. Dehydration depletes the neurohypophysis of its content of ADH, and hydration permits reaccumulation.[912] Gaupp and Scharrer[758] state that secretory droplets formed in the supraoptic nucleus may be traced along axons of the supraopticohypophysial tract and seen to enter the neurohypophysis. They suggest that the hormone is formed in the nucleus and liberated into the blood stream through the gland. In

* Commercial pituitrin (obstetrical) contains 10 units and pituitrin (surgical) contains 20 units of oxytocic activity per cc. Five-tenths of a mg. of standard pituitary powder contains 1 unit of oxytocic and 1 unit of pressor activity. Commercial pitressin contains 20 units of pressor activity and less than 1 unit of oxytocic activity per cc. Commercial pitocin contains 10 units of oxytocic activity and less than 1 unit of pressor activity per cc.

partial confirmation of this view, appreciable amounts of ADH have been reported in the supraoptic nucleus.[441]

Pitressin, even when given intravenously in large doses, has no significant pressor action in man * or lightly anesthetized dogs and rabbits, and indeed it may induce a fall in pressure in part by constriction of the coronary vessels and other actions on the heart, while in anesthetized animals there are considerable species or circumstantial differences. Hence the name 'pitressin' is rather misleading [872, 878, 1312, 1434, 2061, 2271]

Whether the antidiuretic and pressor effects attributed to pitressin are themselves activities of a single molecular species is in doubt. Most investigators have accepted a single principle [748, 874, 1015, 1088, 1324, 1993, 1804] while others [641] have presented evidence that the two activities can be separated

Heller [862] reported that, as judged by the subcutaneous rat test of pituitrin,[898] the antidiuretic factor is more stable than the pressor factor when heated at all pH values between 0 57 and 10 0 He believed that he had obtained a preparation by heating at pH 10 0 which contained only about 8 parts of pressor activity to 100 parts of antidiuretic activity Such non-pressor preparations exert no diuretic action when given intravenously to anesthetized rabbits, hence the diuretic action of untreated extracts was referred to the pressor principle [864] However, Fraser,[691] repeating Heller's work, found that when the subcutaneous rat method was replaced by an intravenous dog method, acid hydrolysis had no differential effect on the pressor and antidiuretic activities His evidence indicates that the differential results obtained by Heller are attributable to differences in the rate of subcutaneous absorption. The balance of evidence seems to favor the view that the antidiuretic and pressor activities are attributable to a single molecular species.

Pitocin and ADH may represent fragments of a single parent molecule Rosenfeld [1904] found that, when untreated press juice from the posterior lobe is subjected to ultracentrifugation, the two activities show very similar sedimentation rates Because of the mild extraction procedure used, he believes that the press juice contains a large molecular species as the native hormone, this molecule having a sedimentation constant about one-half or one-third that of egg albumin Commercial extracts such as pituitrin, pitressin, pitocin, etc, contain the activities in the form of physiologically active cleavage products which are much smaller

* Large, that is, in respect to the production of antidiuresis

in molecular weight. Van Dyke, Chow, Greep, and Rothen [2089] confirm this unimolecular view, and assign the native protein a molecular weight of 30,000. They believe it improbable that this protein is secreted as such into the blood, but think that scission into smaller, physiologically active products probably occurs in the gland.

THE ANTIDIURETIC HORMONE

The antidiuretic hormone is immediate and constant in its action, which is best revealed by its effects upon water diuresis in mammals.* In adequate doses it completely prevents diuresis, regardless of the dose of water, and under its influence marked blood dilution may occur [779] and water intoxication is readily obtained.[2157] The dilution of the blood in rabbits may be sufficient to produce hemolytic anemia.[527, 779]

The excretion of water is delayed for 2 to 10 hr., depending upon the dose of ADH and method of administration. Tolerance is not developed on repeated injection.[1890] The hormone does not delay the absorption of water from the intestine [961, 1138, 1910] and it inhibits the diuresis produced by the intravenous administration of water.[1517, 2128] Denervation of the kidneys does not affect the antidiuretic response to either endogenous or exogenous hormone or modify the development and course of experimental diabetes insipidus.[104, 1138, 1784] Removal of the abdominal sympathetic chain, section of both vagi, antropinization or section of the spinal cord at the upper thoracic or lower cervical level, have no effect upon the development of experimental diabetes insipidus.[656] The hormone exerts its typical action in decerebrate animals [631, 1518] and to some extent in the heart-lung-kidney, in which preparation the urine is typically dilute.[1981, 2105] The antidiuretic action is independent of moderate changes in the creatinine clearance in the hypophysectomized, decerebrate dog.[104] The diuresis normally observed in the heart-lung-kidney is reduced if the blood is switched through the head of a dog with the pituitary intact, but not if the gland has been removed.[2104]

The antidiuretic response in individual rats, measured as the reduction in urine flow during a 20 min. period subsequent to the

* ADH does not accelerate the reabsorption of water in the fishes, frog, and alligator, its action in this respect being evident only in mammals and to a lesser extent in the chicken [294]

intravenous injection of ADH, is a linear function of log dose expressed in microunits.[1072] Pitressin is inactivated by liver tissue *in vitro*, and presumably hepatic destruction is one route of disposal in the body.[610]

From the facts given above, there can be no doubt that the hormone is secreted into the blood and acts directly on the kidney without the intervention of other organs The essential mode of action in man, and doubtless all mammals, is the acceleration of the tubular reabsorption of water, probably in the distal system, for in physiological doses it has no effect upon the rate of glomerular filtration in the dog or man (*vide infra*).

NORMAL RATE OF SECRETION

By the continuous intravenous administration of ADH, Shannon[1162] found that graded antidiuresis is obtained in dogs weighing 10 to 15 kg only in the range of 1 0 to 5 0 milliunits/hr. (0.1 to 0.3 milliunits/kg. per hr.) There is considerable variation in the antidiuresis produced by a given rate of hormone administration in different animals and in any one animal at different times, differences which are perhaps related in part to differences in the rate of filtration and perhaps to variations in intrinsic active water reabsorption, which is in turn related to the state of hydration of the body. The effects of the hormone when given intravenously in minimally effective doses disappear in less than 30 min. The time required for complete recovery increases, though not proportionally, as the rate of hormone administration is increased Prolonged action can be obtained by the subcutaneous administration of larger doses

Minimal urine flow in hydrated dogs is usually reached at 5.0 milliunits hr, and no further decrease is obtained when the rate of administration is raised from 20.0 to 100 milliunits With the larger dose, the urine flow remains the same or increases The reduction in urine flow obtained by hormone administration to normal dogs is frequently less than that obtained by simple dehydration for 18 to 24 hr, even though the urine is consistently more hypertonic in the former circumstance, because during dehydration the filtration rate is decreased, thus decreasing the delivery of electrolytes and water to the distal system, and dehydration

itself may promote active water reabsorption quite apart from the presence of ADH. True oliguria (0.1 cc/min. or less in a 10 kg. dog) is obtained only by a combination of dehydration and hormone administration.

Lauson, Eder, Chinard, Cotzias, and Greif[1218] found that the infusion of pitressin in a 70 kg. man at the rate of 0, 7.5, 16.4, 50, and 333 milliunits/hr. *under conditions of hydrated water balance* produced endogenous creatinine chromogen U/P ratios of 7.2, 80.8, 138, 183, and 134, respectively. Taking a U/P ratio of 138 as maximal for the conditions of the experiment, this would indicate that 0.2 milliunits/hr. per kg. is about the minimal effective dose in man, a figure corresponding to Shannon's figure of 0.1 to 0.3 milliunits/hr. per kg. in the dog.

OSMOTIC DIURESIS

The hormone produces, at most, a slight decrease in urine flow if the urine is already concentrated. More frequently, the urine flow increases (the 'diuretic effect') because of an increased excretion of sodium (the natriuretic effect to be discussed later). It has no or negligible effect on the diuresis produced by sodium chloride, sucrose, glucose, urea, etc., since it is incapable of promoting the further reabsorption of water in the face of proximal diuresis (see ch xx).[83, 1318, 1432, 1504, 1570, 2066] Motzfeldt,[1492] who was the first to recognize this fact, found that, although the hormone might reduce the urine flow in rabbits markedly for several hours, it was impossible to produce anuria by its use. Similar conclusions are to be reached from Buschke's[304] observations on dogs and Poulsson's observations on man.[1654]

ACTION OF POSTERIOR PITUITARY EXTRACTS ON RENAL CLEARANCES

In their experiments on the perfusion of the rabbit's kidney, Richards and Plant[1714] found that relatively large doses of pitressin, like adrenalin, *decreased the renal blood flow at constant perfusion pressure* while increasing the kidney volume and the urine flow. Thermostromuhr measurements showed that, in anesthetized and unanesthetized animals, large doses of pitressin reduced the blood flow through the kidneys, the femoral artery and vein, and the carotid artery and jugular vein, the *reduction* persisting for an hour or more and being independent of sympathectomy and adrenalectomy.[760, 905, 1071] More recent experiments indicate that the effects of pitressin on the renal blood flow vary with the dose and route of administration. Subcutaneously and intramuscularly

the effects are variable, but large doses (0 075 to 0 06 units) intravenously decrease the blood flow.* [1123] In all the experiments above the dosage was unphysiological, so far as antidiuresis is concerned. Shannon [1148] found that the intravenous administration of 1 to 350 milliunits/hr. produced no change in the creatinine clearance in the dog Others (ch. XIV) report no consistent effect upon the filtration rate or renal blood flow in man, rabbits, and dogs (Breed and Maxwell, pers. com.) [104, 794, 411, 1034, 1129] In rats, however, Dicker and Heller [418] report that 3 milliunits of pitressin (Parke Davis and Co.) per 100 gm. body weight, subcutaneously, increases the variability of the inulin and diodrast clearances, as revealed by an increase in the coefficient of variation (σ/mean), without markedly changing the mean values (The same dose of pitocin significantly increases the clearances.) † Undifferentiated posterior pituitary extract (pituitrin) affected these clearances as did pitressin. The authors conclude that the renal vascular effects of pitressin may vary in character according to the concentration of pitressin in the blood

CLEARANCES IN EXPERIMENTAL DIABETES INSIPIDUS

Farr, Hare, and Phillips [418] found that there is no significant difference between the urea clearance of normal cats (14 3 cc/min. per sq m.) and that of cats with diabetes insipidus (13 1 cc/min per sq m.). White and Heinbecker [1155] report that in diabetes insipidus dogs having free access to water the creatinine clearance remains unchanged during the transient phase and interphase, but gradually falls after the first or second week of permanent polyuria, reaching a level of approximately half normal at 4 to 6 weeks, returning toward normal 3 to 6 months after the operation. The urea/creatinine clearance ratio remains normal except for changes related to urine flow until the creatinine clearance becomes depressed, at which time this ratio may rise to 0 8 In some contradiction of these results, Pickford and Ritchie [1013] report that the creatinine clearance remains unchanged after section of the supraoptic tract or removal of the posterior lobe

Shannon [1141] has shown that in both normal and diabetes insipidus

* Reduction of glomerular activity in the alligator and chicken [46] and pithed frog [45] are perhaps peculiar to these forms or attributable to excessive doses. Pasqualini [973] presents unconvincing evidence that ADH promotes tubular reabsorption in the toad

† It seems probable from the available data that a species difference will be revealed in the control of glomerular activity in the rat as compared with the dog and man

dogs dehydration generally reduces the creatinine clearance, presumab through reduction of the volume of the extracellular fluid, the creatinir clearance returning to normal on rehydration. This effect is much mor marked in the diabetes insipidus dog than in the normal animal becaus of the absence of the water-conserving action of ADH. In the former, 18 to 24 hr. of dehydration may reduce the extracellular fluid by one-half or more, with usually a marked reduction in filtration rate. This in turn reduces the load of electrolytes presented to the proximal tubules, which favors more complete reabsorption, and this circumstance, combined with continued water loss, leads to increased plasma osmotic pressure and the withdrawal of water from the cells, a process which helps maintain the volume of the extracellular fluid. Whether fluid equilibrium will be attained, and whether the animal will survive on a restricted water allowance, will depend on the reduction in filtration rate, the intrinsic capacity of the distal tubule to form a hypertonic urine, and, of course, on the availability of water from endogenous or exogenous sources. On return to abundant water intake, the extracellular compartment expands and the filtration rate increases; simultaneously, the conditions favoring reabsorption of water are removed and the polyuric state is re-established. Moderate excess or deficit in water intake, he believes, is compensated for by changes in the distal reabsorption of water, without significant changes in extracellular fluid volume or filtration rate. The administration of water to the diabetes insipidus dog (as to a slightly dehydrated normal dog) increases the filtration rate, which increases the load of filtered electrolytes; the urine flow may increase twofold or more without corresponding dilution, presumably solely because of this increased load. Conversely, during dehydration the urine flow may be decreased to small values without a proportional increase in concentration, because of the decrease in filtration rate and hence in the osmotic load.

Shannon's data show that, when the dehydrated diabetes insipidus dog ingests isotonic saline instead of water, the solution is temporarily retained and the volume of the extracellular fluid is increased; this leads to an increase in the filtration rate, which in turn produces an increase in urine flow not at first accompanied by an equivalent increase in sodium excretion, the concentration of urinary sodium remaining below that of the ingested saline. Loss of water proceeds without a comparable loss of sodium until an increase in the concentration of extracellular electrolyte occurs; this stimulates the thirst mechanism and the animal takes a second drink of saline, and the ingested fluid, being hypotonic, dilutes the extracellular electrolyte and thirst is temporarily satisfied. However,

the ingested saline further expands the extracellular volume and leads to a further increase in the filtration rate, this cycle proceeding until the filtration rate of sodium is in excess of the tubular reabsorptive capacity. Sodium is now excreted in significant amounts but at a urine concentration still below that of the ingested fluid, and hence concentration of extracellular electrolyte again occurs as water is discarded in excess of sodium. After several of these episodes, glomerular filtration is increased to such an extent that the load of filtered sodium considerably exceeds tubular reabsorptive capacity and the sodium concentration of the urine attains that of the ingested fluid. As long as the animal continues to drink the saline solution, it remains in a more or less steady salt and water balance despite marked polyuria. A true steady state is not established, however, since the drinking may be episodic rather than continuous and there is a lag between the drinking of saline and its absorption. Following each drink, a period of high urine flow produces a progressive contraction of extracellular fluid, which finds renal expression in a lowered filtration rate and decreased sodium excretion; the excretion of water in excess of sodium produces an increased concentration of electrolyte in the extracellular fluid and the animal is stimulated to drink again, thus initiating the succeeding oscillation.*

When the animal drinks water, a prompt reversal to the normal state occurs. The elevated filtration rate maintains an excessive tubular load of sodium and promotes sodium excretion, creating a sodium deficit. This process continues until sodium excretion becomes balanced against sodium intake, when the filtration rate and fluid exchange return to a steady state. This description, acceptable in respect to the observed changes in renal function, is possibly deficient in that it neglects changes in the reabsorptive activity of the tubules for sodium, mediated in part by adrenal hormones.

White, Heinbecker and Rolf [2803, 2804] report that Tm_D is not reduced in diabetes insipidus dogs if the anterior lobe is not removed or seriously injured.

Handley and Keller [898] more recently report that, in diabetes insipidus dogs excreting 2500 to 6000 cc/day of urine, drastic reductions occur in the filtration rate, renal plasma flow, and Tm_G, reductions that in most

* An interesting implication of the observations above is that a 'steady state' cannot be achieved by the progressive, uniform excretion of excess sodium or water in accordance with constant renal clearance principles, since an infinite time would be required to reach equilibrium, it appears that this difficulty is resolved here as in other physiological systems (the regulation of respiration, blood pressure, body temperature, etc.) by overcompensation and hence oscillation above and below the steady state as a mean.

animals exceed 50 per cent. These changes occur within 10 days to 2 weeks after operation and persist for more than 2 years. Since the changes in the three functions are approximately proportional, they conclude that reduction in function is due to a decrease in the number of active nephrons, a decrease which *they interpret to be protective.* All three functions can be restored to the preoperative level by infusing saline. *It may be that the dogs were not keeping themselves in fluid* balance, or were not studied under conditions of balance, or, what seems more likely, there was significant injury of the anterior lobe.

EFFECTS OF POSTERIOR PITUITARY EXTRACTS ON ELECTROLYTE EXCRETION

It has long been accepted that pitressin (and ADH) induces chloruresis (increased chloride excretion) by promoting the excretion of sodium (natriuresis). (Chloride has been followed *in many more observations* than has sodium.) This effect is far from invariable, however. The problem *is complicated by the assertion that, in rats, pitocin is sometimes* more effective in this respect than is pitressin.[516, 690, 692, 1178] However, in view of the fact that pitocin produces a significant increase in the filtration rate in rats,[516] it seems unwise at the present time to accept this as a specific tubular effect.*

The chloruretic (or natriuretic) effect of pitressin as a specific tubular effect is rather less debatable, though still equivocal.[106, 692, 1322, 1664, 1732, 1889, 1995, 2245] In 3 out of 4 diabetes insipidus dogs studied by Shannon,[1862] the intravenous administration of pitressin (20 milliunits/hr. or less) *increased sodium and chloride excretion* without a change in the filtration rate, an effect which was reduced when the animals were *moderately hydrated (possibly because of the reduced* [illegible]

excretion sometimes produced a higher electrolyte concentration [illegible] urine during hormone antidiuresis in the diabetes insipidus dog than was usually observed during oliguria at comparable urine flows in the normal dog. Thus the increased sodium excretion sometimes operated to limit *the degree of* antidiuresis or, where large doses were given during the oliguric state, to cause an increase in urine flow. Anslow, Wesson, *Bolomey, and Taylor*[54] *find that in hydrated* normal dogs (where presumably there is a minimal endogenous secretion of ADH) and under conditions otherwise *conducive to stable sodium excretion* and when changes in filtration rate can be excluded, the rate of excretion of chloride

* Species differences may also be involved in the action of pitressin on *sodium* reabsorption.

on discontinuing pitressin infusion (15 to 20 milliunits/hr.) falls to one-half or less the maximal rate during pitressin infusion. Changes in sodium and potassium excretion generally parallel changes in chloride excretion. In experiments with no water load (presumably with maximal endogenous ADH) no significant change in chloruresis was observed when pitressin was administered or discontinued. Pitocin (26 milliunits/hr.) had little or no antidiuretic or chloruretic effect under any condition. They conclude that the pressor-antidiuretic fraction is chloruretic, but that this chloruretic action is demonstrable only when endogenous secretion is minimal (i.e. during water load). Their evidence does not show that the chloruretic action is specifically attributable to the antidiuretic hormone, but it presumably is since this agent predominates over pitocin in the commercial preparation by a ratio of 10 to 1.

Other investigators have failed under various conditions to obtain a chloruretic effect. Hare, Hare, and Phillips [illegible] found that, in diabetes insipidus dogs receiving 2.5 per cent sodium chloride solution at a rate of 10 cc/min., chloride excretion was wholly independent of whether pitressin was infused or of the rate of pitressin administration, although graded antidiuresis was obtained with increasing doses of the latter. They conclude from these experiments and their experience with normal animals that pitressin does not facilitate chloride excretion. Crutchfield and Wood [illegible] report that pituitrin in doses of 20 units had no effect on sodium excretion in man, and the effects of even massive doses of pitressin on chloride excretion in man are reported by Little *et al* [illegible] to be highly variable, sodium excretion sometimes being increased and sometimes decreased. Smith and MacKay [illegible] obtained an increase in the 24 hr. excretion of sodium and chloride in normal subjects with pitressin but obtained negative results in a subject with diabetes insipidus, as did Thorn and Stern,[illegible] who obtained decreased excretion. In the experiments of Barclay, Kenney, and Nutt,[illegible] 1.25 to 2.5 units of pituitrin consistently increased chloride excretion and counteracted the chloride retention which is associated with exercise.[illegible]

EXTRARENAL ACTION OF ADH

Evidence that ADH may act extrarenally in mammals, causing a redistribution of water or electrolytes between blood and tissues, is slight.[illegible] Such changes as may occur in the composition of the blood following ADH administration or neurohypophysectomy can in general be interpreted in terms of water retention or water loss, associated with changes in electrolyte balance issuing secondarily from changes in the filtration rate and natriuresis.[illegible]

animals. Arnold,[61] using the rat method, found equal amounts of antidiuretic activity in the urine of normal and hypophysectomized dogs after dehydration. Harris [818] reports that electrical stimulation in the region of the supraoptic nucleus in the rabbit produces antidiuresis and the urinary excretion of an antidiuretic material. Antidiuretic activity has been reported in the urine of normal men after fainting.[2082] Litschitz and Stokey [1249] report that in dogs the antidiuresis of morphine, presumably mediated through the neurohypophysis, is accompanied by the excretion of an antidiuretic substance in urine. Untreated adrenalectomy was followed by the appearance of antidiuretic activity in the urine of cats,[1411] whether the animals were dehydrated, or hydrated to the point where the plasma sodium concentration was reduced.

The urine of toxemic women appears to contain excessive quantities of some antidiuretic material, as judged by the rat method.[891,2067] Krieger and Kilvington [1170] initially reported antidiuretic activity in urine from normal pregnant, pre-eclamptic, and eclamptic women, but subsequently they questioned the relationship to eclampsia.[1171] Ham and Landis [891] compared the properties of the antidiuretic substance they obtained from the urine of normal, pregnant, and toxemic women with those of pituitrin; the latter was not concentrated by the ultracentrifuge, was chloruretic, and dialyzed through cellophane membranes, the antidiuretic material in the urine differing in all three respects Fresh saline extracts of the posterior pituitary gland were chloruretic and dialyzed slowly. Press juice from the gland was only partially concentrated by the centrifuge. These authors also obtained an antidiuretic substance from the placenta of eclamptic patients which resembled the urine material.

Robinson and Farr [1753] reported antidiuretic activity in the dialyzed and concentrated urine of nephrotic subjects with edema. This material was found on several occasions to disappear with spontaneous diuresis. Ralli, Robson, Clarke, and Hoagland [1671] found that the urine of cirrhotic patients contained large amounts of an antidiuretic substance that was not chloruretic. Smaller amounts of activity were found in dehydrated normal patients and in cirrhotics who had not developed or who had recovered from ascites. The administration of serum albumin to patients with cirrhosis produced no change in the excretion of antidiuretic substance.[1381] Leslie and Ralli [1225] also found antidiuretic activity in the urine of rats whose livers were damaged by high fat diets and who showed blunted water diuresis. Hall, Frame, and Drill [857] have confirmed these observations in cirrhotic patients, but report that normal rats have as much antidiuretic material in their urine as those with liver damage

and, if hydration is maintained, rats with liver damage can have a normal water diuresis. Stueck, Leslie, and Ralli [illegible] have shown that urine concentrates can be adsorbed on permutit and subsequently eluted with acetic acid to give a material which has enhanced antidiuretic potency. These eluates, as well as some concentrates, have caused cessation of urine flow in rats for as much as 300 min., an effect that cannot be duplicated with pituitary extracts. Noble, Rinderknecht, and Williams [illegible] report antidiuretic activity in the urine of a patient with hypertension, achlorhydria, diminished glucose tolerance, and hyperchromic anemia, who was believed to suffer from hyperfunction of the posterior pituitary. Ellis and Grollman [illegible] also report antidiuretic activity in the urine of patients with essential hypertension and in renal hypertensive dogs and rats. Grollman and Woods [illegible] report that oxidation of pitressin by hydrogen peroxide destroys the chloruretic but not the (rat) antidiuretic activity. Increased antidiuretic activity is also reported in the urine of patients with infectious hepatitis,[illegible] and Bergu, Rokaw, and Massie [illegible] report antidiuretic material in the urine of patients in congestive heart failure, as demonstrated by intravenous administration in dogs, but they state that it apparently is not the same substance as commercial pitressin.

Dialyzed dog and human urine is also reported to contain a mildly diuretic substance when tested by intravenous injection in the dog.[illegible]

ANTIDIURETIC FACTORS IN BLOOD

The search for antidiuretic activity in the blood and urine of patients with pre-eclampsia was suggested to Anselmino, Hoffmann, and Kennedy [illegible] by the fact that large doses of pituitary extract coupled with overhydration produce edema, convulsions, and hypertension in dogs, a phenomenon now clearly recognized as water intoxication.[illegible] These investigators reported that collodion ultrafiltrates of plasma from toxemic patients were antidiuretic when injected intraperitoneally into rabbits and pressor in the decapitated cat (in addition the filtrates expanded frog melanophores). Attempts to duplicate this work using the same technique, using the intravenous dog assay method, or using transfusions to normal recipients have all failed to yield positive results.[illegible]

Page [illegible] reported that small amounts of pituitrin added to human blood in vitro and allowed to stand for 30 to 60 min. before transfusion produce a definite antidiuretic response in suitably prepared recipients. By this means he was unable to demonstrate any detectable quantity of antidiuretic material in 500 cc. of blood from normal fasting donors;

animals. Arnold,[63] using the rat method, found equal amounts of antidiuretic activity in the urine of normal and hypophysectomized dogs after dehydration. Harris[819] reports that electrical stimulation in the region of the supraoptic nucleus in the rabbit produces antidiuresis and the urinary excretion of an antidiuretic material. Antidiuretic activity has been reported in the urine of normal men after fainting.[2052] Litschitz and Stokey[1249] report that in dogs the antidiuresis of morphine, presumably mediated through the neurohypophysis, is accompanied by the excretion of an antidiuretic substance in urine. Untreated adrenalectomy was followed by the appearance of antidiuretic activity in the urine of cats,[1411] whether the animals were dehydrated, or hydrated to the point where the plasma sodium concentration was reduced.

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and, if hydration is maintained, rats with liver damage can have a normal water diuresis. Stueck, Leslie, and Ralli[2021] have shown that urine concentrates can be adsorbed on permutit and subsequently eluted with acetic acid to give a material which has enhanced antidiuretic potency. These eluates, as well as some concentrates, have caused cessation of urine flow in rats for as much as 300 min., an effect that cannot be duplicated with pituitary extracts Noble, Rinderknecht, and Williams[1531] report antidiuretic activity in the urine of a patient with hypertension, achlorhydria, diminished glucose tolerance, and hyperchromic anemia, who was believed to suffer from hyperfunction of the posterior pituitary. Ellis and Grollman[599] also report antidiuretic activity in the urine of patients with essential hypertension and in renal hypertensive dogs and rats Grollman and Woods[876] report that oxidation of pitressin by hydrogen peroxide destroys the chloruretic but not the (rat) antidiuretic activity Increased antidiuretic activity is also reported in the urine of patients with infectious hepatitis,[1184] and Berçu, Rokaw, and Massie[121] report antidiuretic material in the urine of patients in congestive heart failure, as demonstrated by intravenous administration in dogs, but they state that it apparently is not the same substance as commercial pitressin

Dialyzed dog and human urine is also reported to contain a mildl diuretic substance when tested by intravenous injection in the dog.[121]

ANTIDIURETIC FACTORS IN BLOOD

The search for antidiuretic activity in the blood and urine of patients with pre-eclampsia was suggested to Anselmino, Hoffmann, and Ken- nedy[53] by the fact that large doses of pituitary extract coupled with verhydration produce edema, convulsions, and hypertension in dogs, phenomenon now clearly recognized as water intoxication[1984] These investigators reported that collodion ultrafiltrates of plasma from tox- emic patients were antidiuretic when injected intraperitoneally into rabbits and pressor in the decapitated cat (in addition the filtrates expanded frog melanophores) Attempts to duplicate this work using the same technique, using the intravenous dog assay method, or using transfusions to normal recipients have all failed to yield positive results[313, 1057, 1171, 1229, 1422, 1562, 2061]

Page[1567] reported that small amounts of pituitrin added to human blood in vitro and allowed to stand for 30 to 60 min. before transfusion produce a definite antidiuretic response in suitably prepared recipients By this means he was unable to demonstrate any detectable quantity of antidiuretic material in 500 cc of blood from normal fastin... wors

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eclamptic urine, resisted nitrous acid) by the same method. Drill and Frame[113] report that as little as 0.1 cc. of crude and pure liver extracts and 'intraheptol' are antidiuretic in rats. (None of these agents has been tested in diabetes insipidus animals to see if it acts by way of the neurohypophysis) Baez, Mazur, and Shorr (pers. com.) have shown that VDM or ferritin, as well as the iron-free moiety of ferritin, are antidiuretic when given intravenously in rabbits and dogs, but this action is apparently mediated by excitation of the neurohypophysis (Moreover, VDM is not excreted in the urine except in severe renal damage)

Neither the role of these materials in human water balance nor their mode of action on the rat kidney has been established The chief evidence for their possible physiological importance is the frequent correlation between antidiuretic activity and edema Although the effect on rats is presumed to be on renal water reabsorption, the decrease in chloride excretion, the occasional complete and prolonged suppression of urine flow, and even deaths of the test animals suggest an accompanying hemodynamic or toxic effect Most disturbing is the recent demonstration (Raisz and Ralli, pers com.) that the antidiuretic substance in concentrates prepared from the urine of patients with hepatic cirrhosis (and in eluates prepared by permutit adsorption of urine from both cirrhotic and normal subjects) is totally ineffective in inhibiting water diresis when given intravenously in large doses to the hydrated dog, although these preparations are very potent in evoking antidiuresis when given intraperitoneally to the rat. In the dog, the material may cause a rise in filtration rate, urine flow, and salt excretion, but water reabsorption is not accelerated

In evaluating subcutaneous and intraperitoneal tests for antidiuretic substances, it must not be overlooked that a painful stimulus can itself evoke strong antidiuretic activity in the dog, and this is presumably true in the rat Almost any subcutaneous injection can be painful, and the intraperitoneal injection of test material in the dog in the writer's laboratory has given evidence of considerable pain. It is pertinent to note that, although maximal water diuresis can be obtained in the dog under chloralose anesthesia, antidiuretic activity can still be induced by a painful stimulus Hence the subcutaneous or intraperitoneal injection of materials of unknown nature into rats with the neurohypophysis intact can yield at best an ambiguous result.

Furthermore, since commercial pituitary extracts have not been demonstrated to be identical with ADH, comparison of antidiuretic materials of unknown nature with pituitrin or pitressin does not in itself answer the question of pituitary origin It seems likely that the antidiuretic

from donors who had received large amounts of pituitrin just before the transfusion, or in 400 cc. of blood from patients with eclampsia or pre-eclampsia. Neither was there any effect on blood pressure. Walker[2223] found antidiuretic activity in rabbit blood during dehydration, using a collodion absorption method, but Hare, Hickey, and Hare,[812] using an intravenous test in dogs, could not show any antidiuretic activity in the blood of dehydrated dogs.

Antidiuretic activity is reported in the serum of hypertensive patients, this activity decreasing after irradiation of the pituitary gland, although the blood pressure is not reduced,[866] and in the serum of pregnant women and pregnant rats, as well as in the serum of rats receiving repeated injections of anterior lobe extract and anterior pituitary-like gonadotropic extract (only one strain of rats proved to be satisfactory). Irradiation of the pituitary inhibited the production of this antidiuretic material. Birnie, Jenkins, Eversole, and Gaunt[176] report that fresh rat serum is antidiuretic by the rat intraperitoneal assay method, and that this activity is enhanced by adrenalectomy. Large doses of theelin, progesterone, testosterone, and antuitrin S did not modify the excretion of antidiuretic material by dehydrated rats.[1410] Transfusion of large amounts of blood from individuals with postsyncopal oliguria has inhibited diuresis in hydrated recipients[288]

Although the posterior pituitary gland is generally implicated in these studies, the source and nature of antidiuretic activity is not established. Both differences and similarities between pituitary extracts and urine antidiuretic material have been reported in respect to inactivation by boiling, neutralization, and strong alkali by many of the above-mentioned investigators, but the absence of chloruresis in almost all studies, the different behavior on dialysis, and Schaffer, Cadden, and Stander's[1774] demonstration that the material in eclamptic urine is sistant to destruction by nitrous acid indicate that it is not identical wi pituitrin or pitressin. The problem is complicated by the fact that mar organic (glutamic acid, arginine, tyrosine, gelatin) as well as inorgani substances (cadmium, nickel, zinc salts) potentiate the action of pitressir in the Burn rat (subcutaneous) test, apparently by slowing adsorption from the site of injection.[828,1532,1774] The antidiuretic and pressor activities of pitressin are increased by boiling with acetic acid.[1545]

Pick[1810] has emphasized the role of the liver in water metabolism, not only as a storage organ but as the producer of diuretic and antidiuretic hormones. Antidiuretic material has been found in alcoholic extracts of minced liver by Theobald and White.[2064] Schaffer, Cadden, and Stander[1774] obtained an antidiuretic material from liver (which, like that in

tion may run ahead of water absorption in producing the hemodilution responsible for the initiation of diuresis [311]

Chambers, Melville, Hare, and Hare,[338] by following the chloride R/P ratio (see footnote, p. 264), the excretion of hormone in the urine, and the inhibition of water diuresis in the test animal,

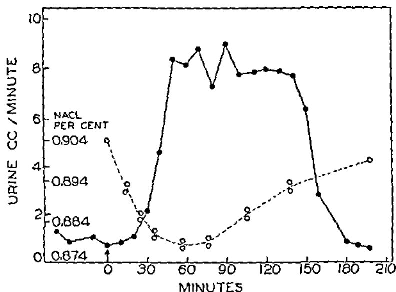


FIGURE 48 Blood dilution and diuresis in man resulting from the ingestion of 1000 cc of water The blood dilution is indicated by the change in vapor pressure in terms of an osmotically equivalent sodium chloride solution (Baldes and Smirk [78])

and comparing the action of hypertonic solutions of sodium chloride, sodium sulphate, and urea, conclude that it is the change in the osmotic pressure of the plasma rather than changes in any specific ingredient (sodium, chloride, etc.) that determines the response of the neurohypophysis

The extent of plasma dilution at the peak of diuresis following the ingestion of 1 liter of water by man amounts to at most 3.5 per cent; if all the ingested water were immediately distributed throughout the body water of a 70 kg man, the expected dilution would be about 2.5 per cent.

material excreted in the urine in dehydration and after salt loading is of pituitary origin, and that the antidiuretic activity of the urine after the intravenous injection of pitressin reflects the excretion of the antidiuretic factor in this preparation But it is clear that the substance in the urine of cirrhotic patients is not ADH, its normal excretion product, or pitressin, despite its antidiuretic activity in rats, since it has no antidiuretic activity in dogs. As the data stand, about the only conclusion to be drawn is that the demonstration of antidiuretic activity in the rat affords no reliable information on the secretion of ADH or its excretion in the urine.

REGULATION OF NEUROHYPOPHYSIAL SECRETION

OSMOTIC PRESSURE OF PLASMA

It is clear that the secretion of ADH is mediated in response to some change in the state of hydration of the body. Earlier investigators were divided on the question whether or not actual dilution of the blood occurred during the degree of hydration which is entailed in ordinary diuresis,[640] but it is now established that such dilution does occur, although the changes are of a very small order of magnitude. The administration of water in large quantities to dogs and man produces a perceptible decrease in the protein content, electrical conductivity, and total osmotic pressure of the plasma, and of the iron, hemoglobin, sodium, and chloride of whole blood. By delicate viscosity measurements to detect changes in protein content of the plasma, and by precise measurements of conductivity to detect changes in electrolyte content, White and Findley[650,2195] and Govaerts and Verniory[830] confirm the view of Priestley, Rioch, Baldes, and Smirk, and other investigators cited by them, that diuresis following water ingestion results primarily from an increase in the mol fraction of water in the plasma * (fig. 48). When water is administered *per os*, sodium chloride moves into the dilute intestinal contents during the early part of the absorptive period and this intestinal migra-

* The distinction between water content of plasma and mol fraction of water is important Thus the percentage content of water in plasma (gm of water per 100 gm of plasma) is increased by addition of a slightly hypertonic salt solution, while the mol fraction of water (fraction of total number of molecules and ions present represented by water molecules) is decreased The latter determines the colligative properties of a solution, it is proportional to the aqueous vapor pressure and hence to the osmotic pressure

tion may run ahead of water absorption in producing the hemodilution responsible for the initiation of diuresis.[611]

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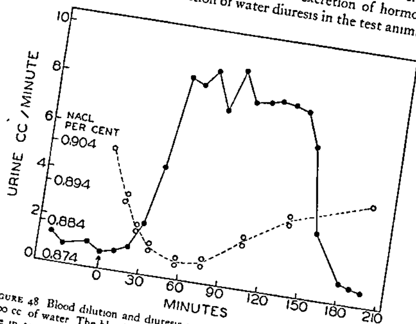


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The extent of plasma dilution at the peak of diuresis following the ingestion of 1 liter of water by man amounts to at most 3.5 per cent, if all the ingested water were immediately distributed throughout the body water of a 70 kg. man, the expected dilution would be about 2.5 per cent.

Gilman and Goodman [780] first used the administration of hypertonic sodium chloride in rats (50 cc/kg. of 5 per cent solution) to stimulate the release and urinary excretion of the antidiuretic hormone, and, as judged by the presence of antidiuretic material in the urine, they concluded that dehydration combined with the intravenous injection of 10 per cent sodium chloride could increase the rate of hormone liberation in cats as much as 100-fold. The administration of salt decreases the amount of ADH in the rat's pituitary and increases by fifteenfold the number of mitoses in the pituicytes,[117] and rats kept on a diet deficient in water for 5 to 7 days show a large decrease in the content of both the pressor and oxytocic principle. Fasting for a week, fighting, electrical stimulation, forced muscular work, adrenalectomy, and the administration of large amounts of isotonic saline for several days do not influence either the pressor or oxytocic activity of the gland.[1897]

In an exquisite series of experiments, Verney [2107, 2108, 2109] has shown that antidiuresis can be evoked in dogs by the injection into the carotid artery of hypertonic solutions of sodium chloride, sodium sulphate, and sucrose in quantities too small to have an effect when given intravenously. His results indicate that the osmoreceptors are bilateral and supplied by blood from the internal carotid arteries. The osmoreceptors, when perfused unilaterally, are activated by an increase of 8 mg/100 cc. of chloride, or 2 per cent increase in the osmotic pressure of the blood, and fail to show adaptation during a perfusion period of 40 min., although on other grounds slow adaptation over a matter of days is to be expected. Presumably an increase of 1 per cent would be effective during bilateral perfusion. The rate of hormone secretion during antidiuresis induced by intracarotid perfusion corresponds to 1 microunit/sec., and suffices to reduce the urine flow to substantially less than 1 cc/min. Glucose is less effective than sodium chloride and sucrose, presumably because the osmoreceptors are to some degree permeable to this substance; an increase in blood glucose of 90 mg/100 cc. fails to elicit an antidiuretic response on prolonged infusion. Urea is also without any effect, presumably because the osmoreceptors are freely permeable to it. Findley [641] has pointed out that the paraventricular nucleus and, more par-

ticularly, the supraoptic nucleus have an unusually rich blood supply, suggesting a chemoreceptor function. Verney tentatively suggests that the osmoreceptors may comprise a number of vesicles, ranging in diameter from 10 to 100 μ, located in the supraoptic nucleus, the total unilateral surface area of which is of the order of 1 sq. mm.

Even allowing for the characteristic delay between maximal hydration of the body and maximal diuresis, the rate of urine formation is not invariably proportional to the degree of hydration of either tissues or blood, and an almost normal diuretic response may be obtained when the tissues and blood are dehydrated,[960] or when the osmotic pressure of the blood has previously been elevated by salt administration.[18] On the other hand, the reduction of the osmotic pressure by chronic salt depletion does not of itself induce diuresis. It would appear that it is not the absolute value of osmotic pressure but a relatively rapid change in that value which produces the diuretic response. In any case, it may be anticipated that the response of the osmoreceptors will to some extent be conditioned by the pre-existing state of the blood, i.e. they will display adaptation comparable to the 'set of the center' evident in other integrated neurologic phenomena. No simple explanation, however, serves to explain the presence or absence of water diuresis under all circumstances (Addison's disease, cardiac failure, cirrhosis, and other conditions frequently characterized by hyponatremia), and other factors can as yet only be adumbrated.

Hickey and Hare [993] have used hypertonic saline in man to test the functional capacity of the neurohypophysis, noting both the R/P ratio and the decrease of water diuresis in the recipient, and have demonstrated that 1 of 3 subjects with mild polyuria showed a normal response to this test and excreted an antidiuretic substance in the urine. By removal from pitressin therapy this subject's water exchange was reduced to normal, and it was concluded that her polyuria was the result of polydipsia.

WATER DIURESIS AND DELAY TIME

By a variety of methods, numerous observers have shown that the peak of diuresis does not occur until well after the maximal hydration of

plasma.*[650,1730] The delay time between the peak of blood dilution and maximal diuresis in dogs and rats is 15 to 20 min.[960,1135,1518] and averages 37 min. in man.[650] This delay between maximal hydration and maximal diuresis is still evident when water is given intravenously,[1517] but it is reduced in rats by the repeated administration of water.[35,1163]

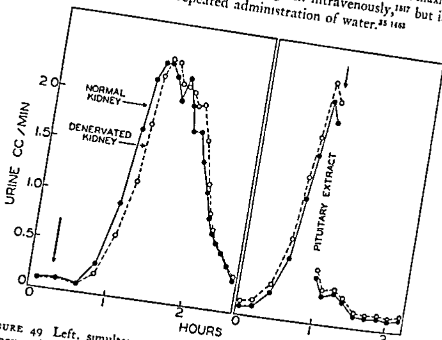


FIGURE 49 Left. simultaneous diuretic response of normal and denervated kidney in dog to water *per os* Right effect of pituitary extract subcutaneously. (Klisiecki, Pickford, Rothschild, and Verney [1188,1189])

A series of observations by Baldes and Smirk[76] on a subject who had drunk a liter of water is shown in figure 48. These authors report that the maximal decrease in total osmotic pressure is reached in 25 to 45 min. after water ingestion and amounts to 1.5 to 2.75 per cent.

Dogs weighing 10 kg. absorb 250 cc. of water in 36 min.[1188] or 40 cc/kg. in 40 min.,[488] cats 40 cc/kg. in 35 min.,[1011] rats 50 cc/kg. in 30 min.[961] Anesthesia delays intestinal absorption.[961]

* This interval is, of course, longer when one adds the time required for intestinal absorption. In the dog, diuresis does not begin until 40 min. and maximal diuresis is not reached until 50 min. or more after water administration,[34,888,1135] the average interval between water administration and peak of diuresis in 5 dogs averaged 102 min. before, and 95 min. after destruction of the supraoptic nuclei, in 3 other dogs this interval was 105 min. before, and 110 min. after hypophysectomy.[1616,2193]

Klisiecki *et al.*[1138] concluded that the delay between maximal hydration of the body and maximal diuresis is attributable to the time required for ADH to disappear from the blood. They found that the delay time is reduced in a diuretic animal and increased in a dehydrated animal, and Pickford[1682] showed that when pituitary extract is administered in constant doses the degree of inhibition of water excretion is roughly inversely proportional to the existing water load in the body, a result that is consonant with the belief that the total antidiuretic effect is due to the summation of the endogenous and exogenous moieties of hormone.*

If it is supposed that the osmoreceptors show adaptation to the osmotic pressure of the plasma, as suggested above, the fact that water output always returns to normal sooner than does the osmotic pressure of the plasma[2198] may be attributable to this adaptation.†

PHYSIOLOGICAL MEDIATION OF DIURESIS AND ANTIDIURESIS

Klisiecki, Pickford, Rothschild, and Verney[1135] exteriorized the ureters of a dog so that the urine from each kidney could be collected separately. They observed that the response of the two normal kidneys during water diuresis is generally closely parallel, though one kidney may occasionally lag behind or run ahead of the other throughout the diuretic response. This parallelism in response has been observed by others in the dog[993] and in man (Michie, pers. com.)[869, 788] Why a difference in the temporal response of the two kidneys ever exists is unexplained.

* Shannon,[1682] however, has observed the same phenomenon in diabetes insipidus dogs, and suggested that the intrinsic activity of the distal tubule and therefore the susceptibility to the antidiuretic hormone varies with the water load. Summation may involve endogenous hormone, intrinsic tubular activity, and exogenous hormone.

† The view that delay time is related to destruction of endogenous hormone has been criticized by White and his coworkers,[illegible] who find in man that the same average interval (83 min.) intervenes between the ingestion of water (1000 to 1500 cc.) and the crest of diuresis, whether it is the first drink or a second following shortly after an initial diuretic response. (Paradoxically, one subject showed no lag between water absorption and increased urine output with a first drink, possibly because of an anticipatory conditioned reflex.) White and his coworkers also point out that the time relations of the response to a large dose of water are not significantly altered in diabetic animals, a point also noted by Pickford and Ritchie.[1815] Although these arguments against Verney's position cannot all be answered at this time, some of them do not seem particularly cogent and need not be reviewed in detail.

That renal denervation does not produce diuresis in the normal, unanesthetized dog has been repeatedly demonstrated (ch. XIV), and unilateral denervation does not produce diuresis on the de-

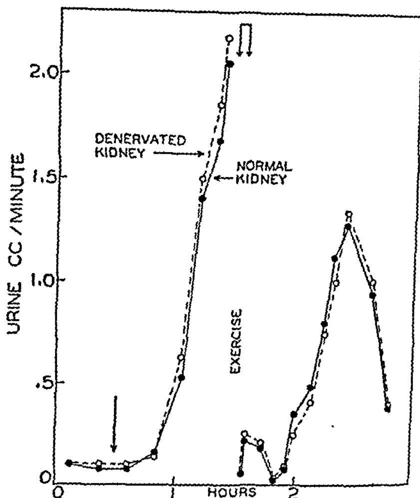


FIGURE 50 Simultaneous response of normal and denervated kidney in the dog to water diuresis and exercise. (Klisiecki, Pickford, Rothschild, and Verney [118])

nervated side in man.[798] Denervation diuresis is observable only in anesthetized animals or under conditions where it may be assumed that there is vasomotor excitation from circulatory inadequacy or other causes, and it then represents release from

neurogenic or adrenergic vasoconstriction.[447,1929] The renal nerves play no part in water diuresis in hypophysectomized and decerebrate dogs.[104] Denervation of one kidney does not affect the diuretic response to water as compared with the control, either quantitatively or in respect to time relations, nor does denervation affect the response to ADH, as is shown in figure 49.

A variety of circumstances can prevent water diuresis by inducing reflex secretion of ADH or by vascular changes in the kidney.[1614] Thus diuresis is abruptly arrested by vigorous muscular exercise in both dog and man, the innervated and denervated dog kidneys responding in an identical manner (fig. 50). The antidiuretic effect in the dog diminishes with repetition, indicating central conditioning [1638] The effect in man is not invariable [579] and, if marked, is accompanied by reduction in renal plasma flow and filtration rate.[82,441] Noxious or painful stimuli * evoke an equivalent antidiuretic response in the innervated and denervated kidney.[2063] Adrenalin and the sympathetic nervous system play a part in this response, but antidiuresis may occur without changes in renal blood flow and in splanchnisectomized dogs.† [1788 2106 2108] Antidiuresis is evoked in rabbits anesthetized with chloralose-urethane by painful stimuli before but not after destruction of the pituitary stalk, and stimulation of the intact stalk has a similar effect [931] Antidiuresis is also evoked in rats by the so-called 'alarm reaction' elicited by nearly lethal doses of adrenalin, cold, formaldehyde, etc.[1091] Syncope associated with the prolonged maintenance of the passive erect posture is accompanied by oliguria of abrupt onset and lasting for 15 to 90 min.; here there is moderate reduction in the filtration rate but the evidence also indicates increased secretion of ADH. Transfusion of blood from subjects with postsyncopal oliguria to water-loaded subjects is reported to reduce diuresis in the latter.[280,281,282,283 284]

* Emotional stress was produced by sounding an electric motor horn near the animal, and pain by faradic stimulation through needle electrodes inserted into the subcutaneous tissue of the flank, the strength of stimulus in each case being just enough to cause definite resentment

† Renal ischemia produced by compression of the renal artery produces an immediate cessation of urine flow but recovery is also immediate (1 to 4 min) on removal of the arterial clamp, whereas after exercise, etc., recovery of diuresis requires some 30 to 60 min [1788]

O'Connor and Verney [1535] have shown that the antidiuretic response evoked by noxious stimuli is abolished or largely reduced by removal of the posterior lobe (fig. 51). The stalk and infundibulum were left intact, and, by quantitative comparisons of the response before and after operation relative to the response to known quantities of hormone, these investigators conclude that the residual functional tissue in their operated animals, which is adequate to prevent the permanent phase of polyuria, amounts to about 5 per cent of the normal. The quantity of ADH normally required

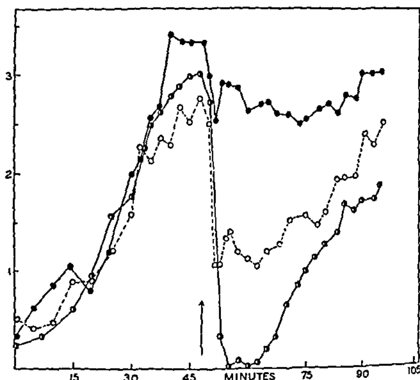


FIGURE 51 Inhibition of water diuresis by emotional stress in the dog. Three hundred cc. of water were given at zero time. Ordinates show the rate of urine excretion over the interval before each plotted point, the intervals being usually 2 5 min At the arrow the dog was excited for a period of 1 min. by a weak faradic current through needle electrodes in the flanks. Half-dots, control, solid dots, 26 days, open dots, 32 days after removal of the posterior lobe. (O'Connor and Verney [1538])

to inhibit water diuresis in the dog is of the order of 1 milliunit,* which agrees with Shannon's conclusion that graded diuresis is obtained by the intravenous administration of 1 to 5 milliunits/hr.†

O'Connor and Verney [1414, 2108] report that faradic stimulation of the flank during water diuresis sometimes evokes a rapid, transient inhibition attributable to vasoconstriction in the kidneys;‡ after denervation of the adrenals and the kidneys this transient inhibition is replaced by the prolonged inhibition typical of ADH. The presence of both types of inhibition in any one experiment is variable, and only after the exclusion of the adrenals and the renal nerves does the typical ADH inhibition appear consistently. ADH inhibition can be prevented by the injection of adrenalin or tyramine just before faradic stimulation. Since these substances do not diminish the antidiuretic action of exogenous hormone, the authors conclude these substances inhibit the pituitary secretion which would otherwise be evoked by afferent nerve stimulation, and that variability in sympathetic activity explains the absence of ADH inhibition in some tests and its presence in others.

The intravenous administration of acetylcholine to unanesthetized dogs causes antidiuresis (with chloruresis), while in dehydrated (oliguric) dogs acetylcholine causes diuresis (with chloruresis). These effects disappear after posterior lobectomy, indicating that acetylcholine evokes secretion of ADH. The effect is not blocked by atropine, which places it in the category of nicotine-like effects of acetylcholine.[1613] Nicotine itself is antidiuretic in the normal but not in the hypophysectomized rat. This antidiuretic activity is also evident in man, and sufficient nic-

* Burroughs Wellcome 'Infundin' was used and standardized to contain 10 international oxytocic units/cc. One milliunit signifies the antidiuretic activity of 10^{-4} cc. of this extract.

Hart and Verney [97] calculated that spontaneous diuresis in man is due to a fall in the concentration of ADH to less than 1 part of hormone in 15,000,000,000 parts of plasma.

† Assuming that the hormone is restricted to the blood stream by adsorption on plasma protein, 20 cc. of dog's blood at the height of antidiuresis would contain only 0.03 milliunits, since the Burn rat test will not detect less than 2 milliunits, this test is obviously inadequate to detect physiological changes in the hormone concentration of the blood.

‡ The author and his coworkers have observed a comparable phenomenon in man where urethral catheterization was painful, i.e. a marked and persistent decrease in filtration rate and renal blood flow accompanied by oliguria.

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The diuretic response to alcohol differs markedly in one respect from the response of the cerebral cortex The latter is most affected by the rate of increase in blood alcohol concentration; the greater this rate of increase, the greater the disturbance of function at any absolute concentration. The diuretic response, on the other hand, is dependent mainly on the duration of increasing blood alcohol concentration, and not on the rate of increase. The naturally slow absorber, therefore, tends to give a larger diuretic response than the rapid absorber.

At equilibrium, the U/P ratio of alcohol per unit of water is close to 1.0 Apparently the tubules, at least the distal tubules and the collecting ducts, are freely permeable to it.*

Bader, Eliot, and Bass [73] have studied the phenomenon of 'cold' diuresis (exposure to 15° C.) and found no change in endogenous creatinine chromogen clearance or renal plasma flow Diuresis is inhibited by standing and by walking and readily inhibited by pitressin, and so resembles simple water diuresis that the authors infer that it represents diminished secretion of ADH

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Repeated flashes of bright light at brief intervals cause diuresis over a period of 3 hr. in rats, a reaction which does not occur if the eyes are covered [74] The authors believe that optical stimuli acting over the optico-hypothalamico-hypophysial pathway disturb the secretion of water-balance factors from the neurohypophysis Acceleratory force, either positive or negative, suppresses urine formation in rats during application and is followed by transient diuresis which is inhibited by ADH. Repeated daily exposures to acceleratory forces for about three weeks

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mal used.[647, 606, 629 630 963, 1249 1614, 2062, 2141] Though absorption from the gastrointestinal tract may be delayed by the anesthetic, this does not account for the inhibition of diuresis, which is still present when water is given intravenously.[961 1517] Fee [629] suggested that in the normal animal there is some mechanism that inhibits the secretion of ADH, and that under anesthesia this inhibition is removed and secretion released.

Morphine (2 5 to 5 0 mg/kg of sulphate either subcutaneously or intravenously) is particularly effective in inhibiting water diuresis in the normal dog, as demonstrated by de Bodo [458] This inhibition is not diminished in dogs with 1 adrenal removed and the other denervated and demedullated, or by atropinization It is independent of any effects upon gastrointestinal activity, and is evident only if some part of the neurohypophysis is functionally intact Since morphine does not potentiate the action of exogenous antidiuretic hormone, de Bodo concluded that it brings about the increased secretion of ADH either through a 'release phenomenon' or by direct stimulation of some part of the hypothalamico-hypophysial system Physostigmine potentiates the action of morphine, indicating that this action is mediated by acetylcholine. Morphine does not inhibit saline diuresis, or inhibits it to a lesser degree than water diuresis Handley and Keller [898] confirm the antidiuretic action of morphine in normal dogs, but find that it is also effective in dogs with high stalk section and diuresis amounting to 3 to 4 liters/day *

Kraushaar *et al* [1161] deny that morphine acts via the pituitary mechanism in normal women, but, as de Bodo points out,[489] the two women with alleged diabetes insipidus who were tested with morphine and showed antidiuresis must have had considerable neurohypophysial tissue, because their urine output was well below that of established diabetes insipidus

Phenobarbital sodium given intravenously either in full (0.08 gm/kg) or half-anesthetic (0.04 gm/kg) doses also inhibits water diuresis in normal dogs, but the inhibitory effect is less marked than with morphine Avertin, amytal, phenobarbital, and pentobarbital are similarly active but to a much less degree. Like morphine, the barbiturates do not exert an inhibitory effect on water diuresis unless some part of the neurohypophysis is intact [490 493] Diuresis is inhibited in rabbits by urethane, luminal, paraldehyde, and chloroform.[953, 961] The only anesthetics of record that appear to have no inhibitory effect on water diuresis are chloral hydrate and chlorosane (chloralose),[490, 2062] the latter has been

* This may reflect secretion from residual secretory tissue in the median eminence

lead to albuminuria and pathological changes in the kidney, believed to be referable to renal anoxia[1894]

The water intake of rats is automatically adjusted to water output through the thirst mechanism, even as water output is adjusted to water intake through the supraopticohypophysial mechanism. When output is reduced by the administration of pitressin, the intake of dilute food is promptly reduced, the urge to ingest fluid being stopped by the accumulation of water in the body. When one and one-half kidneys are excised in rats, maximal water diuresis is greatly decreased but recovers within 4 weeks after operation to a rate two-thirds as rapid as before. The intake of fluid food is decreased for only a week, at which time intake and output have returned to control values.[31]

Dicker[311] has shown in rats that water diuresis is marked by three phases: (a) the absorptive period preceding the onset of diuresis and characterized by a dilution of the plasma accompanied by a decrease in the sodium and chloride concentration of both plasma and tissues and a decrease in the extracellular fluid volume; (b) the excretory pe riod, corresponding to the height of water diuresis, accompanied by a increase in the sodium and chloride concentration of muscle and a d crease in potassium, and resulting in an increase of the extracellul fluid volume and a decrease in intracellular fluid; (c) the terminal riod during which all the values above return to normal. In hypop teinemia, water diuresis is delayed and blunted because plasma d tion is diminished, the water accumulating in the extravascular compartments.

Weller[2163] has attempted an analysis of the extracellular and intracellular water in the cortex and medulla of the rat kidney during dehydration, water diuresis, and saline diuresis He assumes that chloride is confined to the extracellular fluid, an assumption which is not supported by the studies of Ljungberg,[1256] and that the tubular urine is identical in chloride content with the bladder urine, an assumption which is unwarranted The derived data cannot confidently be accepted.

Studies in overall water balance in several mammals, cold-blooded animals, and invertebrates under a variety of conditions have been compactly summarized by Adolph[29]

EFFECTS OF ANESTHESIA ON THE NEUROHYPOPHYSIS

It is well established that anesthetics and related drugs (ether, chloroform, paraldehyde, urethane, amytal, barbital, morphine, codeine, dicodid, nembutal, demerol, etc.) reduce or prevent water diuresis, the effect varying with the anesthetic, the depth of anesthesia, and the ani-

were made upon animals in a state of anesthesia. The use of sedatives and anesthetics has vitiated many observations in physiology, but in no field has it led to more confusion than in the present one. Investigators have learned that anesthetized animals may be highly abnormal and that the results obtained on them have little bearing upon the normal, and they are using their talents to develop methods which as far as possible can be used upon unanesthetized animals, without more pain, psychical or physiological disturbance than need be caused in man for the same purpose.

Another complication is presented by choice of species for experimental work; the rabbit is unsatisfactory because of the ease with which renal ischemia is induced, with resulting interdependence between urine flow and filtration rate;[265] the common animal most closely resembling man is the dog, but even here there are differences in glomerular dynamics, susceptibility to diet, etc., of which the investigator should be aware.

Lipschitz and Stokey [1249] have recently adduced evidence from which they argue the existence of three different mechanisms of antidiuresis (1) the secretion of ADH, (2) nervous control of the kidney (in the rat), and (3) a humoral antidiuretic factor in the dog other than ADH In respect to (1), they find that, in both dog and rat, ADH, acetylcholine and phenobarbital inhibit water diuresis in both the innervated and denervated kidney, phenobarbital showing no antidiuretic activity in neurohypophysectomized dogs, morphine, while inhibiting water diuresis, simultaneously causes an increased urinary excretion of antidiuretic substance in the dog. These results are all consonant with the simple neurohypophysial theory. With respect to (2), they find that in rats with denervated kidneys, although pitressin and phenobarbital are still antidiuretic, morphine loses most of its diuretic action, indicating that in this species morphine antidiuresis may be attributable in part to renal vasoconstriction They state that the rat, unlike the dog, does not excrete an increased quantity of antidiuretic substance under the action of morphine. In respect to (3), ADH, acetylcholine, and phenobarbital do not inhibit the diuresis caused by sodium chloride, melamine, formoguanamine, or caffeine. It is well known that ADH will not inhibit saline diuresis and there is no reason to expect acetylcholine or phenobarbital to do so It is conceivable that melamine and formoguanamine, when given during oliguria, increase the urine flow by elevation of the filtration rate or natriuresis, and in such a case it is not to be expected that ADH, acetylcholine, or phenobarbital would have an antidiuretic effect. Morphine inhibits formoguanamine diuresis

recently used in water diuresis studies on dogs in the writer's laboratory with apparently maximal diuresis and no complications.

THE ALLEGED DIURETIC ACTION OF PITRESSIN

It is typical of the history of this complicated problem that the first observations on the action of pituitary extracts upon urine formation, reported by Magnus and Schafer [1367] in anesthetized animals, indicated (falsely it is now seen) a diuretic action. During the next 15 years numerous investigators confirmed this, and it was not until 1913 that the characteristic antidiuretic action was noted independently by von den Velden and Farini, to be confirmed quickly by many investigators.[1318, 1482, 1942] In 1917, Motzfeldt [1482] presented evidence that the diuretic action was a physiologically fallacious phenomenon due to unsuitable conditions of observation.

In anesthetized animals there is increased if not maximal secretion of ADH; * the urine is maximally or nearly maximally concentrated and, in some cases, the filtration rate is reduced, contributing to oliguria. In such animals posterior pituitary extracts may cause a rise in blood pressure and changes in glomerular activity,† as well as an increased excretion of sodium chloride. These two effects operate against the antidiuretic action of ADH to produce a moderate increase in urine flow. Such 'diuresis' as is obtained in oliguric, unanesthetized dogs may be attributable to chloruresis alone.[1862] There is no evidence for the existence of a truly diuretic principle in any part of the pituitary gland (including the pars anterior) and the essential action of the only hormone related to water excretion so far isolated from the neurohypophysis is an antidiuretic one.

It is unfortunate that so many early observations on renal function

* The oliguria observed in water intoxication [854, 1090] may in part be due to the release of excessive ADH.

† Pituitrin has a 'diuretic' effect in rabbits anesthetized with morphine and urethane and already rendered diuretic by the intravenous infusion of sucrose or by phlorizin, the 'diuretic' effect being accompanied by a parallel increase in filtration rate.[1402] However, since both morphine and urethane lead to increased secretion of ADH, and since sucrose diuresis, or glucose diuresis in the phlorizinized animal, elicits proximal diuresis, since glomerular activity is highly sensitive to sympathetic excitation in this species, and since pitressin may influence the excretion of sodium chloride as well as glomerular activity, these experiments are difficult to interpret. In the normal rabbit, ADH exerts a typical antidiuretic action.[1482]

The effects of small and large doses of pituitrin in mice [1104] are uninterpretable because of possible vasomotor and chloruretic actions of pitressin and pitocin.

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both rat and dog; in the rat this antidiuretic action has already been interpreted by the authors as largely vascular in nature, hence (if true) this presents no paradox. In the dog, the 'diuretic' action of formoguanamine is so small (0.18 to 0.24 cc/min. over the control period) that the alleged antidiuretic action of morphine is scarcely demonstrated. Sodium chloride diuresis increases the urinary excretion of an antidiuretic substance, whereas no increased excretion occurs during melamine, formoguanamine, or caffeine diuresis. This is to be expected if the last three compounds produce glomerular diuresis or induce chloruresis. The fact that morphine causes an increased excretion of antidiuretic substance during formoguanamine diuresis is not incompatible with its action in the normal animal. Hence the evidence presented by Lipschitz and Stokey is inadequate to challenge the simple pituitary theory.

CONDITIONED REFLEXES INVOLVING DIURESIS

Marx[1412] and others have shown that diuresis can be induced in man by hypnotic suggestion. It has further been shown that dogs repeatedly given water under constant circumstances may respond with diuresis, even in a denervated kidney, to a conditioned stimulus when this is applied *unaccompanied by water*,[310,311,312,626,677,1418,1614] while Eagle[659] has shown that the normal diuretic response to water may be inhibited by a conditioned reflex Although the higher centers are not necessary for either the induction of diuresis or the action of ADH,[680,681,1070,2104] it is clear that the supraopticohypophysial system has abundant connections with the brain stem and cerebral cortex, and consequently the effects of drugs such as caffeine, theophylline, adrenalin, morphine, alcohol, *etc.*, as well as circulatory changes such as syncope, shock, and fever, must be interpreted cautiously.

A disturbing element in the neurohypophysial theory is the recent assertion by Bykow, cited by Gantt,[745] that conditioned reflex inhibition of urine formation can still be obtained in a dog hypophysectomized by the ring method (diabetes insipidus ?) unless the kidney is denervated. The implication is that the conditioned reflex operates by such profound renal vasoconstriction as to lead to oliguria. If confirmed, this indicates that a conditioned reflex may be more powerful in inducing renal vasoconstriction in this species than are many severely noxious stimuli The demonstration of renal vasoconstriction after afferent stimulation of a painful nature is of course not new; the role of the sympathetic nervous system in the oliguria produced by noxious stimuli has been discussed by Rydin *et al.*,[1758] Verney,[2106,2108] and Pickford.[1614]

ROLE OF THE PARS ANTERIOR, THYROID, AND OTHER GLANDS IN DIABETES INSIPIDUS

One point which has been a nexus of confusion in all experiments on diabetes insipidus is the role of the anterior pituitary gland At one extreme is the majority opinion that full and permanent polyuria does not develop after total hypophysectomy, when presumably all parts of the pituitary, including the anterior lobe as well as all neurohypophysial tissue, have been removed At the other extreme are those who contend that anterior lobectomy does not interfere with the development of polyuria, and that the failure of others to obtain it is attributable to the circumstance that a protective vestige of functional neurohypophysial tissue has been left in the animal. In between are a variety of opinions in regard to the direct or indirect influence of the anterior lobe, the function of this organ involving, as it does, nearly all other endocrines.

Von Hann in 1918 stated on the basis of her clinical experience that polyuria develops in man when the posterior lobe is destroyed only if pars anterior tissue is left, and this conclusion has been affirmed experimentally by many investigators Careful distinction must be made between the so-called transient phase and permanent polyuria The effects of anterior lobectomy are probably not immediate, no matter how mediated, and polyuria may be maintained for a short period in completely hypophysectomized animals Nearly all investigators agree, however, that with time the polyuria diminishes or disappears as the loss of the anterior lobe comes to be felt, i e the anterior lobe is necessary for the maintenance of maximal polyuria (For a fuller review of the literature see Fisher *et al* [656]) [104, 166, 384, 658, 947, 949, 1584, 1724, 1813]

There may be species differences in the effects of anterior lobectomy, polyuria apparently being less reduced in the rat than in the cat,[433, 829, 436, 810, 2082, 2189] but the present evidence is inadequate to answer the question Heinbecker and White [945, 949] contend that full diabetes insipidus follows total hypophysectomy, including removal of the anterior lobe (pars distalis), as proved by serial sections of the hypothalamus and of sellar contents or of decalcified sella with contents. Over a period of months the diabetes recedes, however, a circumstance which they attribute to slow atrophy of the adrenals and thyroid They state that when sufficient thyroid and desoxycorticosterone are administered simultaneously to the totally hypophysectomized dog, the additional administration of anterior lobe extract decreases the urine output, rather than increasing it They believe that the presence of the anterior lobe

may permit polyuria to occur in the presence of a slight residuum of functional neurohypophysis (median eminence, etc.), which, in the absence of the anterior lobe, would suffice to prevent the development of polyuria, and they attribute the conflicting results obtained by others to incomplete removal of neurohypophysial tissue. Keller[1105,1106] similarly contends that a small functional remnant of neurohypophysial tissue is able to prevent polyuria in the absence of the anterior lobe, but that if all this tissue is removed, characteristic polyuria will develop in the absence of that lobe. The presence of the anterior lobe, however, intensifies this polyuria. He further believes that secretory tissue is present in or near the anterior hypothalamus and that ablation or destruction of this tissue is necessary to obtain polyuria.

Removal of the anterior lobe, with or without destruction *of the neurohypophysis*, diminishes the diuretic response to water, and water intoxication is easily obtained[384,1081,1815] Although Pickford and Ritchie[1815] report that the reduction in water diuresis precedes the reduction in filtration rate, changes in glomerular-tubular balance must be weighed carefully in interpreting blunting of water diuresis, as must also diminished function of the adrenal cortex (ch. XII).

The administration of anterior lobe extracts to normal dogs produces polyuria,[183,2066,2197] and restores polyuria in hypophysectomized dogs and cats;[624,1104,2197] such extracts appear to be less effective in hypophysectomized rats,[1564,2184] though some investigators report a positive result and conclude that the diuretic action in rats is unrelated to growth and appetite responses.[1813]

Thyroidectomy has no effect on the fluid exchange of otherwise normal *animals*, and the *administration of thyroid* produces at most a mild diuresis,[949,1369,1666,2197,2199] although thyroid and hyperthyroidism increase the rapidity of development and maximal rate of water diuresis and increase resistance to water intoxication.[270,765,1136]

However, thyroidectomy markedly reduces, although it does not abolish, polyuria in diabetes insipidus dogs, cats, and rats, and thyroid administration to such animals restores polyuria, while thyroid adminis*tration tends* to increase polyuria *in diabetes insipidus* and may induce polyuria in operated animals in which diabetes insipidus is latent (*fig. 52*).[188,268,384,666,947,949,1058,1104,1369,1370,1666,2197] The effect of thyroidec- [illegible] rate since [illegible] ble ac- [illegible] reduces the water exchange in some types of clinical diabetes.[illegible] This effect

of thyroid is absent in rats after hypophysectomy, even when combined with anterior lobe extract.[1081, 1812, 2189, 2197]

In connection with the role of the thyroid in diabetes insipidus, attention may be called to an observation of de Bodo and Marine.[497] All diabetes insipidus dogs that lived over 4 years showed at autopsy a very small thyroid, which was, however, histologically normal in having cu-

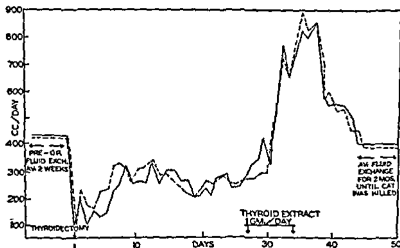


Figure 52. The effect of thyroidectomy and of the subsequent feeding of thyroid on the fluid exchange of a cat with diabetes insipidus The solid line represents the urine output, the broken line the fluid intake. (Fisher, Ingram, and Ranson [686])

boidal epithelium This situation is in contrast to that seen in hypophysectomized animals (i e with the anterior lobe removed) where the thyroid remains of normal size, but on histological examination the epithelium of the gland proves to be flat and of the non-functioning type All the diabetes insipidus dogs in these experiments had a well-functioning anterior lobe, as shown by their response to insulin, adrenalin, fasting, etc The significance of this thyroid atrophy in long-surviving diabetes insipidus animals is not clear. It may represent a compensatory adjustment.

Anterior lobe extract does not increase the water exchange of thyroidectomized or *thyroidectomized-hypophysectomized* dogs, but it does produce a marked diuretic response if maintenance doses of thyroid are

given. It is White and Heinbecker's[947,2197] belief that the anterior lobe contains a principle which is ineffective in the absence of the thyroid but which is not the thyrotrophic hormone, since thyroidectomized and thyroidectomized-hypophysectomized dogs fail to respond to anterior lobe extracts when thyroid is not administered but do respond on maintenance doses of thyroid. Brull[270] reports that kidneys from thyroid-treated dogs, when transplanted simultaneously with control kidneys to a donor anesthetized with chloralose, excrete more urine and give a larger response to normal saline infusion and to hypophysectomy than do controls. However, Hare and his colleagues[914] report that prolonged administration of thyroid raises the threshold of the renal tubules in diabetes insipidus dogs from 0 5 to more than 20 microunits of ADH and they believe that this decreased sensitivity to ADH contributes to the diuretic action of thyroid in latent diabetes insipidus. This explanation, however, would apply to hypophysectomized dogs only if one assumes the presence of some residual antidiuretic tissue, such as Keller[1106] believes is present in the anterior hypothalamus

It has been suggested that the 'diuretic' effect of the anterior lobe is mediated through the adrenal cortex,[433,434 1893,1894] but Schweizer, Gaunt, Zinken, and Nelson[1813] have shown that adrenotrophic preparations are antidiuretic in long-term hypophysectomized rats; they will not prevent the subsidence of the initial polyuria which follows hypophysectomy, and salt-free adrenal cortical extract and desoxycorticosterone acetate have no effect on fluid balance. Failure to correct the effects of hypophysectomy in diabetes insipidus dogs by adrenal cortical extract and desoxycorticosterone are reported by others.[1813,2242] The adrenal cortex is, however, involved in the blunting of the diuretic response to water in hypophysectomized rats, a phenomenon which is repaired by cortical extract or desoxycorticosterone[1081]

Castration and ovariectomy have no effect on diabetes insipidus[656] It is alleged that the administration of estradiol benzoate to man decreases water output, whereas anterior lobe extract increases it, the action of the former compound being attributed to inhibition of anterior lobe secretion.

These views seem to be far apart but it may be concluded that, although the absence of the anterior lobe diminishes the severity of polyuria, this gland is not immediately necessary for the production of diabetes insipidus. The important point is that the anterior lobe secretes a powerful renotrophic hormone, in the absence of which the filtration rate (as well as renal blood flow and tubular excretory function) is markedly reduced (ch. xv) and that in the face of a substantial reduc-

tion in filtration rate it is impossible to obtain a typical water diuresis. The conflicting results in this problem are doubtless attributable to differences in the degree to which the filtration rate has been reduced in various animals, the completeness of destruction of the neurohypophysial tissue, and other incidental factors.

The further examination of the problem requires a quantitative study of glomerular-tubular balance after various operative procedures. The anterior lobe and thyroid have both been shown to have profound trophic effects upon the kidney, increasing the filtration rate and tubular activity (Tm_D, Tm_G) when administered in excess, and renal function is significantly depressed in absence of either gland. Anterior lobe extracts appear to be relatively ineffective in the absence of the thyroid (or thyroxin). The adrenal cortex profoundly affects renal function by upsetting salt and water balance and perhaps in other ways, while the metabolic load of nitrogen and salt delivered to the renal tubules profoundly affects the magnitude of diuresis. Until examination of these variables is completed, it seems best to avoid the term 'diuretic' in connection with the anterior lobe because it implies that this gland participates in a positive rather than a permissive manner in maintaining polyuria and that it acts in specific opposition to ADH. The present evidence does not conclusively establish either view.

CLINICAL DIABETES INSIPIDUS

Diabetes insipidus may appear in man as a result of the pathologic or traumatic destruction of the supraoptic nucleus, in which case there may be some involvement of the anterior lobe, although, if the latter is severe, polyuria fails to develop The disease also appears as an inheritable character, generally without evidence of anterior lobe involvement. Forssman,[673] who reviews the rather complex features of hereditary transmission (the disease is apparently inherited in more than one way), speaks of polyuria when the regular output of urine exceeds 2000 cc., though in most hereditary cases the output in young adults is 8 to 12 liters, rarely as high as 28 liters/day. In some 50 per cent of clinical cases on an unrestricted diet, the urine volume averages under 8 liters/day, in 27 per cent between 8 and 12 liters, and in 22 per cent over 12 liters[109] A small number of cases (5 to 15 per cent) of the hereditary type are definitely refractory to posterior lobe extract, a circumstance which on the present evidence would indicate lack of

responsiveness on the part of the renal tubules,[164,165,673] or neurogenic or psychogenic polydipsia.

Not all patients with diabetes insipidus can be controlled by antidiuretic preparations; in some, thirst is not greatly affected and they continue to drink large quantities of water during therapy. On the other hand it is reported that the antidiuretic hormone may relieve thirst in 20 min even without the administration of water,[1579] but psychic effects were not controlled in this study. Fisher *et al.*[856] believed that, in view of the possibility of psychic effects, such cases could not be accepted as evidence for the primacy of polydipsia. They cite the experiments of Kunstmann, who found that after the ingestion of 10 liters of water daily for many days he suffered from torturing thirst when he attempted to discontinue the experiment It is possible that by virtue of excessive drinking thirst may take on a compulsory character which is either psychically conditioned or secondary to changes in salt metabolism. These authors conclude that the fact that a small number of patients with diabetes insipidus are refractory to treatment with antidiuretic pituitary preparations cannot be accepted as a crucial argument against the view that this disorder is basically due to a deficiency of ADH. In this connection, however, attention should be called to the report that during a period of diabetes insipidus in a patient with transient polyuria, the patient's serum contained a substance that inhibited the action of ADH in the rat test, while, during the period of recovery, an antidiuretic factor was present in excess. The pitressin-inhibiting substance was not found in the serum of 2 patients with chronic diabetes insipidus.[1764]

In 7 subjects with diabetes insipidus studied by Winer [2234] the filtration rate, renal plasma flow, and filtration fraction appear to have been within the normal range when, in the antidiuretic phase, they were maintained by therapy with pituitary extract. The subcutaneous administration of pituitary extract (unspecified) produced a transient decrease in diodrast and inulin clearances with a rise in filtration fraction, an acute effect which subsided in 15 to 20 min, the inulin clearance returning to the control level, the diodrast clearance to values above the control level despite persistent antidiuresis. Comparison of function with and without medication indicated that during uncontrolled diuresis the diodrast clearance may range from 20 to 60 per cent below the clearance during medication, a fact probably referable to dehydration.* The

* Winer's belief that the extraction ratio may be reduced is controverted by his evidence on Tm_D and by the experimental evidence of White and his coworkers [2203, 2204]

inulin clearance and diodrast Tm remained relatively constant in both phases No correlation existed between diodrast clearance, inulin clearance, and urine flow during developing diuresis.

In one subject studied by Williams and Henry [2225] the filtration rate was 106 cc., the renal plasma flow 450 cc., Tm_D 27.7 mg iodine and Tm_G 417 mg. The patient was initially allergic to pitressin but, after desensitization, large doses of pitressin had little effect on water excretion Other members of the patient's family had had polyuria. The fault was apparently genetic, transmitted by females, and appeared during infancy in males. No antipitressin factor could be demonstrated in this patient's plasma, and the authors infer that polyuria represented a congenital deficiency in the distal tubule.

A peculiar case of polyuria is reported by Dyggve and Samsoe-Jensen [556] A boy, aged 12 years, had suffered from excessive thirst and polyuria (4 liters/day) since the age of 2 to 3 years Serum calcium, phosphorus, plasma protein, and bicarbonate were normal, and urologic examination was negative During the Addis concentration test, the urine had a specific gravity of 1 004. The inulin clearance was 11 7 cc/sq m. (17 per cent of normal) and the urea clearance 13 to 15 cc On simultaneous determination the whole blood urea/plasma inulin clearance ratio was 1.03 (assuming 45 per cent cells, 70 per cent water in the cells, and 8 per cent protein in the plasma, the plasma clearance ratio would have been about 0 9) The diodrast clearance was less than 100 cc, and the inulin/diodrast clearance ratio was about 0.20. The recorded inulin U/P ratios ranged from 4 to 5 Only the remarkably low filtration rate could have kept this patient in water balance and alive. From the data one may suspect severe injury of the distal tubules, with possibly some impairment of proximal reabsorption

A low salt diet decreases urine flow, as in experimental diabetes insipidus, while a high salt intake increases it, in both instances with no change in sensitivity to ADH Desoxycorticosterone acetate produces a positive sodium balance with gain in weight, but does not materially reduce urine volume [1319]

The effects of pregnancy upon the disease are variable [197]

Beaser [109] has analyzed the relation between urine volume and solute excretion in mosm/day of patients on various diets, and finds a fair linear correlation of the type

$$V = V_0 + S \text{ mosm.}$$

where V is the urine volume in liters/day, S proportionality a constant, mosm the sum of the milliosmolar equivalent of nitrogen and sodium

chloride excreted in the urine and V_0 an intercept on the V axis. S and V_0 range widely in different individuals, but the author suggests that the relationship is characteristic of each patient; the greater the value of V_0 the greater the excess water requirement independent of dietary load. S he conceives as representing a basic distal tubular concentrating pattern characteristic of each patient.

Changes in protein concentration and colloid osmotic pressure in diabetes insipidus [863] are rather too complex to interpret at the present time.

Aqueous solutions of pitressin have long been used to control diabetes insipidus in man, and recently pitressin tannate in oil (subcutaneously) has been recommended, since the antidiuretic action is prolonged some 24 to 96 hr.[440, 852, 858, 1973, 2003, 2078] Zinc salts have a similar effect.[2002]

CHAPTER XI

Excretion of Sodium and Other Strong Electrolytes

FLUID COMPARTMENTS OF THE BODY

In previous chapters emphasis has been placed chiefly on the excretion of waste products or foreign substances which are destined to be completely removed from the body, or on substances, such as glucose, for which the kidneys constitute a barrier preventing wasteful excretion. As we turn to the consideration of electrolytes, emphasis must be redirected from processes of excretion to processes of conservation and to the specific role of the kidneys in the regulation of the composition and volume of the body fluids.

Water is the chief constituent of the blood, body fluids, and tissues, and in reptiles, birds, and mammals the kidney, supplemented by the thirst mechanism, is the chief effector organ that regulates the concentration of water in the body by virtue of its capacity to excrete greater or lesser quantities of this substance.

The most fundamental consideration in this connection is the supposition that water, after distribution in the circulating plasma, moves freely into all tissues of the body and that, under conditions of equilibrium, it is distributed in such a manner that the vapor pressure (or osmotic pressure) of all tissues and internal body fluids is the same, except in so far as a difference may be maintained dynamically by hydrostatic pressure or tissue tension.

The digestive secretion of water is itself of a considerable order

of magnitude, as is shown by Gamble's[726] estimates quoted in table IV.

TABLE IV

Approximate 24-hour Quantities of Digestive Secretions

Blood plasma volume	3500 cc
Saliva	1500 cc.
Gastric secretion	2500 cc.
Bile	500 cc.
Pancreatic juice	700 cc.
Intestinal secretions	3000 cc
	8200 cc.

However, in most discussions of 'body water' these digestive secretions need not be considered, since no large quantity of fluid is present in the digestive tract at any one moment. For most purposes, the cerebrospinal fluid and secretions of the serous cavities can also be neglected. We are then left with three nominal compartments: the plasma fluid; the interstitial fluid and the intracellular fluid; the plasma and interstitial fluid together comprising the extracellular fluid. Numerous methods, at best approximations, have been used in the past to estimate the volume of these compartments, but recent investigations center attention upon the dye T-1824 for the measurement of plasma volume, inulin for the measurement of extracellular fluid volume, and heavy water (D_2O) for the measurement of total body water. The intracellular fluid volume is calculated by difference.

Data on these three compartments in dog and man are given in table V.[122, 749, 751, 1808, 1809, 1810, 1811]

TABLE V

Distribution of Body Water in Per Cent of Body Weight

	Plasma volume	Extracellular *fluid volume*	Intracellular *fluid volume*	Total body water
Method	T-1824 space	Inulin space	By difference	D_2O space
Dog	5 54 *	19 4	43 6	63 0
Man	4 31 †	16 0	37 0	53.0 ‡

* Average figure cited from Hopper *et al*[1032]
† Average figure cited from Gibson and Evans[773]
‡ Average figure cited from Berger *et al*[122]

Osmotic work on water is apparently never done within the confines of the body. The lymph, tissue fluids, gastrointestinal secretions, bile, cerebrospinal fluid, etc., are all essentially isosmotic with the plasma. The only exceptions to this rule are the saliva and sweat, both of which are hypotonic. The hypotonicity of the sweat possesses the physiological advantage of conserving sodium chloride, and the hypotonicity of the saliva is perhaps related to the role of this secretion in the control of water ingestion through the mechanism of thirst.

That water is uniformly distributed throughout the body in relation to osmotic pressure has been said above to be a supposition rather than a demonstrated fact. If the salivary and sweat glands can elaborate a hypotonic secretion, it is conceivable that at least some cells could metabolically maintain a positive or negative gradient in osmotic pressure between the cytoplasm and the interstitial fluid Indeed, it seems that such is actually the case in those cells in the renal tubule responsible for the elaboration of a hypertonic urine. The available information indicates, however, that the distribution of water throughout the body is conditioned by osmotically active substances [490]

The mere fact of the uniform distribution of water does not place any limitation upon the actual volume of water in the body as a whole or in any one of the fluid compartments. We are concerned with two problems: first, the regulation of the composition of the body fluids, and, second, the regulation of their volume through variation in the absolute quantity of solute (primarily sodium with its attendant anions) retained in the body. Retention or loss of sodium will lead to retention or loss of water and hence to expansion or depletion of extracellular fluid, without offense to the isosmotic principle.

The plasma serves as a medium for the transportation of water and solutes to all the tissues, or, more properly speaking, to the interstitial fluid, which separates the vascular bed from the tissues. Within the plasma is the subsidiary compartment of the blood cells. Between the blood cells and the plasma only a limited interchange of solutes occurs, so that in effect it is the plasma which is directly presented to the kidneys and upon which these organs operate.

The interstitial fluid, lying between the plasma and the tissues, is in almost free communication with the plasma, since all the diffusable constituents of the latter pass readily through the capillary endothelium, and it is by virtue of this free communication that the plasma is enabled to maintain continuous interchange between different tissues. The great speed of interchange between the plasma and the extravascular fluid is indicated by the fact that, as measured with D_2O, 73 per cent of the water in the blood is exchanged with extravascular fluid every minute in the guinea pig,[662] while, as measured by sodium[24], 60 per cent of the plasma sodium and 13 per cent of the extravascular sodium are transferred in either direction per min.,[1437] while 64 per cent of the plasma chloride is exchanged with extravascular chloride. That filtration plays a more important part than diffusion in this exchange is indicated by the fact that sulphate and sodium are distributed at about the same rate.[1871]

Less than 30 min. are required from essentially complete distribution of tritiated water in the body water of rabbits, and approximately 1 hr. in man.[1661]

Interchange between interstitial fluid and plasma is limited in only one respect: the capillary endothelium is poorly permeable to the plasma proteins and, since these with their attendant base are osmotically active, a limitation is thereby placed upon the free migration of water. Where the hydrostatic pressure of the plasma in the capillary tends to force water out of the vascular bed, the osmotic pressure of the plasma proteins (oncotic pressure) tends to draw water back into the vascular bed; were the hydrostatic pressure reduced to zero all the water of the interstitial fluid would theoretically be drawn into the vascular tree by the protein oncotic pressure; or, in the face of resistance to expansion of the plasma (or vascular volume) this movement would proceed until developing hydrostatic pressure came to equal oncotic pressure. Hence, the movement of water and its ultimate distribution between the capillary and the interstitial fluid are determined by the balance between hydrostatic and oncotic pressure. This generalization was formulated many years ago by Starling and, although difficulties arise in applying it in special instances because

of other superimposed factors, its fundamental validity cannot be impugned.[1374]

It is particularly important to note that the circumstances are generally such that filtration of water occurs in the arterial end of the capillary and reabsorption in the venous end (fig. 53), and that

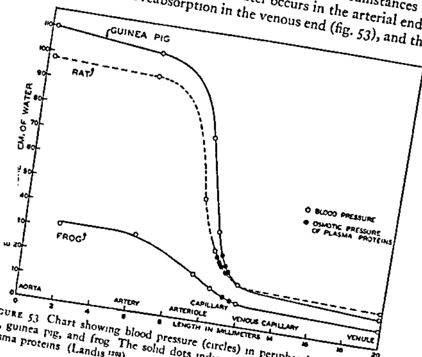


FIGURE 53 Chart showing blood pressure (circles) in peripheral vessels of the rat, guinea pig, and frog. The solid dots indicate the osmotic pressure of the plasma proteins (Landis [1200])

the point of filtration equilibrium (hydrostatic = oncotic pres-ure) will shift toward or away from the venous end as capillary ressure is increased or decreased by dilatation or constriction in e arteriolar and metarteriolar bed. Although detailed knowledge - not available, it may be accepted that local vasomotor tone, under the control both of the nervous system and of humoral agents, plays an important part in determining the absolute quantity of interstitial fluid in any area. Thus, both the circulatory system and the kidneys are concerned in the regulation of the volume of interstitial fluid.

Beyond the interstitial fluid there is the compartment or compartments of the tissues. Between the tissues and the interstitial fluid there is such a *restricted interchange of electrolytes that for* most purposes they may be considered as isolated from each other except in respect to water itself. The restriction is applicable in two senses: first, in respect to the speed of interchange of cations and, second, in respect to their ultimate distribution. *The rate of* interchange of radioactive potassium between red cell and plasma is relatively slow and highly variable. Human red cells show 40 per cent exchange in 12 hr. *in vivo*, and the rate is even slower in the dog, while cat erythrocytes exchange 45 per cent of their potassium per hr.[1495] The erythrocyte exchange rate of potassium is lower in all mammals studied than is the exchange rate of sodium.[1875] When injected intravenously in the dog, about 9 hr. are *required for potassium and 24 hr. for sodium to reach equilibrium* or at least stable distribution throughout the body.[1230]

In the second sense, the ultimate distribution of cations is unique; the base of the tissues consists mostly of potassium and magnesium, there being little sodium in most tissues. That other electrolytes, however (chloride, bromide, thiocyanate), do penetrate some tissues to some degree is now generally accepted, the most recent evidence being derived from the so-called volume of distribution of radioactive isotopes as compared with the volume of distribution of inulin.[760, 1230, 1811] The data in table VI indicate that

TABLE VI

Gross Distribution of Sodium and Potassium in the Normal Dog[1230]

	Sodium mEq per liter of water	Potassium mEq per liter of water	Σ mEq per liter of water
Extracellular fluid	146	4 0	150
Intracellular fluid	35	115	150

about 20 per cent of the exchangeable sodium (exclusive of bone sodium) in the body is intracellular.

The nature of all the osmotically active particles within the cell that account for the intracellular osmotic effect is not known. The sum of the cations within the cell may not safely be used as an index of intracellular osmotic effect, despite the fact that they add

up to about the same molarity in the tissues as in the extracellular fluid. Redistribution of water between intracellular and extracellular fluids occurs in dogs treated with adrenal hormone or adrenalectomized, and the changes observed seem to be greater than can be explained in terms of electrolytes alone.

As has been said above, the regulation of the osmotic pressure of these compartments does not *per se* impose any limitation upon their respective volumes; so long as the vapor pressure of water is maintained uniformly, each compartment remains free to vary in volume. It must be concluded, therefore, that some regulation is superimposed upon the volumes of the plasma, interstitial fluid, and intracellular fluid independently of the regulation of their composition. There seems to be no better view than to suppose that in the tissues the number of osmotically active constituents is regulated by those as yet unknown processes which determine cell structure and other fixed cell characters, in a manner analogous to the regulation of cell volume in unicellular organisms. The regulation of the volume of the interstitial fluids and the plasma, on the other hand, is effected in part by the dynamic factors discussed above, by the regulation of the plasma protein concentration, and, no doubt, by tissue tension and other obscure factors, coupled with the active participation of the kidney.

The writer previously stated his belief that 'the kidney itself is not concerned with whether 2 or 5 liters of plasma are circulating in the vascular bed, so long as that plasma has the proper composition. And this organ, in attempting to regulate the composition of the plasma, will frequently enlarge or reduce the volume of that fluid, and, indirectly, of the interstitial fluid, beyond physiological limits, and sometimes to fatal excess.' [128] It is true that the kidney generally operates to regulate the composition of the plasma first, but the statement above must be corrected because in our present view the kidney is directly concerned in the regulation of the volume of the body fluids, perhaps chiefly the extracellular fluid, and thereby, if indirectly, the plasma.

ELECTROLYTE COMPOSITION OF THE PLASMA

The electrolyte pattern of the plasma is made up typically of the constitutents shown in table VII. The sum of the inorganic or fixed

bases is greater than the sum of the inorganic acids because about 22 mEq. of base are combined with the polyvalent protein anions or with organic acids. Sodium and potassium exist in a freely diffusable state in the plasma, as shown by the fact that their distribution between plasma and pleural, peritoneal, and subcutaneous

TABLE VII

Composition of Typical Human Plasma

(Gamble;[738] Margaria[128].)

Base	mEq/l.	Acid	mEq/l.
Na^+	142	Cl^-	103
K^+	5	HCO_3^-	27
Ca^+	5	$HPO_4^=$	2
Mg^+	3	$SO_4^=$	1
		Organic	6
		Pr^-	16
			155
Total	155		

Osmotically equivalent NaCl solution, gm/100 cc. of water:
Men 0.9447, probable individual deviation: ±0.00495
Women: 0.9269, probable individual deviation: ±0.0059
Freezing point lowering (Δ)
Men: −0.553° C
Women: −0.543° C.

fluids is consonant with the Gibbs-Donnan equilibrium.[869] Calcium exists in the plasma in three forms, the first of which is a protein complex and not diffusable, the second is diffusable organic salts, and the third is ionic calcium. No data are available for magnesium. All the inorganic anions are believed to be freely diffusable.

The total electrolyte composition of the plasma is one of its most finely regulated features, despite the fact that the kidneys operate independently on the individual electrolytes and on water. Gamble and his associates [748] long ago suggested that the adjustments involved in the regulation of the acid-base balance of the blood have as their chief end the preservation of a constant total fixed base, but to the writer the terms 'fixed base' would seem to

indicate merely an arithmetic addition. The physiological desideratum is more probably either the ionic strength or the osmotic pressure of the plasma[1929] The former enters into and influences the reactivity of all *electrolyte systems, and therefore of* all physiological systems, and it is not difficult to imagine that the conservation of sodium, for example, is subordinate to this physi-

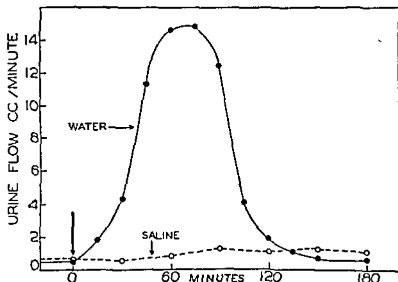


FIGURE 54. The diuretic response in man to 1000 cc. of water or, alternatively, 1000 cc of 1 per cent sodium chloride solution, ingested at zero time. In this experiment 92 per cent of the water was recovered within 180 min. (Smith[1928])

cal-chemical determinant. The evidence is clear that the conservation of water is immediately subordinated to the maintenance of a constant osmotic pressure in the plasma, but the evidence indicates that water conservation is both subsequent to and subordinate to the retention or rejection of sodium. Changes in osmotic pressure from the normal are corrected by the retention or rejection of water and not of sodium. From another point of view, it must be recognized that the conservation of sodium, the chief element in the fixed base and, thus, secondarily of water, is over the long run related or subordinated to the regulation of the extracellular fluid volume. So long as the osmotic pressure is preserved,

there is little immediate resistance to expansion of extracellular fluid volume because the regulatory mechanisms concerned with volume are more sluggish than are those which are concerned with composition. This difference is illustrated by the long-recognized difference in human response to the ingestion of water and of isotonic salt solution, as shown in figure 54. Water produces, after a short interval, a copious diuresis, the extra water excreted in a few hours being equal to the ingested volume. But, when isotonic salt solution is administered to man either *per os* or intravenously, little diuresis occurs; both the salt and water may be retained in the body for hours or days In the latter instance, there is little change in osmotic pressure of the plasma and the salt solution remains distributed throughout the extracellular fluid. On the other hand, if sodium is lost from the body, water will rapidly be sacrificed in the interests of constant osmotic pressure, and restitution of body fluid volume cannot be made until the salt deficit is corrected. Hence, in acute stresses (vomiting, diarrhea, excessive sweating, excessive salt loss or intake, partial renal failure, etc.), regulation of composition takes precedence over regulation of volume, leading to what Gamble called 'the mendicant position of the body fluids.' This mendicant position is largely a matter of rapidity and sequence of adjustment rather than physiological priority. The organism can apparently tolerate changes in volume better than changes in composition of the body fluids. But the relative importance of sodium *per se*, of fixed base, of ionic strength, of osmotic pressure, and of body fluid volume in this pattern of regulation cannot be assessed at the present time.

THE EXCRETION OF SODIUM

The excretion of electrolytes presents numerous complexities that do not enter into the excretion of non-electrolytes, for here we are dealing not with independent molecular species but with paired ions, the individual excretion of which is usually conditioned by some other obligation.

In view of the nature of strong electrolytes it is incorrect to treat any pair of ions, such as sodium and chloride, as though they existed in the plasma or urine in the form of a molecule. Yet because these two are frequently the predominant ions in both

plasma and urine, and because chloride always carries with it an equivalent quantity of cation, mostly sodium, we frequently but incorrectly speak of sodium chloride as a physiological entity. Because the analytical methods for chloride are simpler than those for sodium, nearly all investigations concerned with the excretion of sodium have, until the introduction of the flame photometer, followed the behavior of chloride, under the assumption that it is accompanied by an equivalent quantity of sodium. It is safer, where the nature of the cation is unknown, to designate the unidentified base as B^+.

The necessity of maintaining equivalent quantities of cations and anions in the blood and urine imposes a limitation upon the independent excretion of ions of any one charge. Within this limitation, considerable substitution of various ions is possible Interchangeability is particularly evident in the case of chloride and bicarbonate Loss of hydrochloric acid by vomiting may cause half the chloride to be replaced by bicarbonate and other anions. Vigorous exercise may replace half the bicarbonate with lactate. Increase in carbon dioxide tension may raise bicarbonate at the expense of chloride, while reduction of carbon dioxide tension may have the reverse effect Accumulation of keto acids during fasting or in diabetic acidosis may replace bicarbonate with the anions of these acids. Except as such substitution may cause a change in pH and carbon dioxide tension and thus lead to respiratory embarrassment, they apparently occasion no immediate distress. Indeed, chloride appears to play no specific role physiologically. By repeated centrifugation of blood and replacement of plasma by sulphate solution, Amberson, Nash, Mulder, and Binns [10] were able to reduce the plasma chloride in cats to 7 mM/liter, and to raise the plasma sulphate to 100 mEq/liter, while Hiatt,[112] by the repeated intravenous administration of sodium nitrate, was able to reduce the plasma chloride to 32.7 mEq/liter. In such animals the chloride concentration of the heart, stomach, lung, muscle, kidney, and other tissues and fluids, with the exception of the cerebrospinal fluid, was reduced proportionally below normal. From these studies, it appears that chloride is a physiologically indifferent ion. When sodium chloride is administered, the two ions may, over relatively short periods of time, be excreted at quite dif-

ferent rates because of readjustment of other anions and cations.[805]

Interchangeability is much less evident on the side of the cations, sodium, potassium, calcium, and magnesium; the normal concentrations of the last three *are so small, relative to sodium,* that permissible substitution extends through only a small absolute range.

PROXIMAL REABSORPTION OF SODIUM AND WATER

The data cited in chapter II show that chloride is present in the capsular fluid of the Amphibia in approximately the same concentration as in plasma, *implying the complete ultrafiltration of* both sodium and chloride. We may assume that the glomerular *filtrate carries its full complement of these ions, subject only to* the conditions of a Gibbs-Donnan equilibrium arising from the presence of protein on one side of the glomerular membranes.*

In the Amphibia,[2136] reabsorption of water occurs along the proximal tubule to yield a glucose (phlorizinized) U/P ratio of *c.*1.40, indicating that about 30 per cent of the water of the glomerular filtrate has been reabsorbed (see fig. 2); the facts that *the chloride U/P ratio and the osmotic U/P ratio both remain at* 1.0 (see fig. 1) show that sodium and chloride are reabsorbed *pari passu* with water. In the distal tubule, sodium and chloride are removed from the urine to yield a hypotonic urine essentially chloride-free.

The micropuncture studies of Walker, Bott, Oliver, and MacDowell [2131] (figs. 4 and 5) show that the situation is qualita*tively similar in rats and guinea pigs* Creatinine is concentrated to a U/P ratio of 2.5 half-way down the proximal tubule (the most

* In a membrane system permeable to electrolytes but impermeable to proteins, at equilibrium the electrolytes will be distributed unequally on the two sides. Where the system contains a *number of diffusible monovalent* ions and an ionized salt of protein, NaR, the Gibbs-Donnan equilibrium may be written in the form of an equality of ratios of ion concentration.

$$\frac{[Cl^-]_1}{[Cl^-]_2} = \frac{[HCO_3^-]_1}{[HCO_3^-]_2} = \frac{[Na^+]_2}{[Na^+]_1} = \frac{[K^+]_2}{[K^+]_1}$$

For mammalian plasma and glomerular filtrate, the Donnan factor for chloride, $[Cl^-]_F/[Cl^-]_P$, and bicarbonate, $[HCO_3^-]_F/[HCO_3^-]_P$, may be taken as 1 02,[980] for sodium, $[Na^+]_F/[Na^+]_P$, as 0 95, and for potassium, $[K^+]_F/[K^+]_P$, as 0 90 [669] at 6 gm. of protein per 100 cc. of plasma.

distal point available in the mammalian kidney), but the authors calculate that by the end of the proximal tubule this ratio would reach 5.0, which would mean that 80 per cent of the glomerular filtrate had been reabsorbed. Since the urine remains isosmotic with the plasma, it follows that as much sodium has been reabsorbed as water. For reasons not clear, the chloride U/P ratio rises early in the proximal tubule to 1.4 and remains at this value throughout the first half of its length.*

Final sodium chloride reabsorption, to make a sodium and chloride-free urine, apparently occurs in the distal tubule (or collecting ducts) of the mammals, as in the Amphibia. It is apparently also in the distal tubule (or collecting ducts) that final reabsorption of water occurs to yield a hypertonic urine.

The difficulty in speaking of a sodium or chloride 'threshold' lies in oversimplification † The excretion of sodium (and chloride) is conditioned by a number of factors such as filtration rate, plasma sodium concentration, the natriuretic effect of ADH, and possibly one or more actions of adrenal cortical hormones on the

* Walker *et al* suggest that the chloride U/P ratio rises to 1.4 because chloride replaces bicarbonate as the latter is reabsorbed from the tubular urine; this suggestion implies that bicarbonate (with sodium) is reabsorbed more rapidly than is sodium paired with chloride, and that bicarbonate reabsorption in the proximal tubule is complete. At best, however, assuming 110 mM. of chloride and 25 mM. of bicarbonate per liter in the glomerular filtrate, if chloride replaced all bicarbonate the final concentration of chloride would be 135 mM/liter, which, allowing for the Donnan effect, would give a U/P ratio of $(110 + 25)/110 \times 1.02$, or 1.25 The observed ratio of 1.4 must have some other explanation

† Various investigators have attempted to define a 'threshold' for plasma chloride, because the urine may at times be practically chloride (and sodium) free. Thus Aitken[illegible] observed that, when the plasma chloride in man is reduced below 95 mEq/liter, excretion is fairly constant at about 5 mg. of sodium chloride per hr Rehberg[illegible] also found that, when the plasma chloride falls below 106 mEq/liter, excretion is small and essentially constant. At higher plasma levels he believed that excretion, which may be substantial, is markedly affected by the rate of urine formation, but the converse proposition, that the sodium chloride load of the urine may have affected urine flow in his experiments, must be considered MacKay and MacKay[illegible] showed that essentially chloride-free urine is usually excreted by the rabbit at plasma chloride levels below 85 mEq/liter, although, on other occasions, chloride excretion at this or lower levels may be substantial, a circumstance they attributed to the simultaneous excretion of potassium Equally important is the fact that ammonia will carry chloride into the urine independently of sodium excretion.

tubular reabsorption of this ion, and a simple definition of 'threshold' is even less possible than in the case of glucose. The problem of how sodium excretion is regulated can be approached only by a detailed analysis of all the factors involved.

The first of these is sodium reabsorption in the proximal tubule, where the greater fraction of both sodium and water is reab-

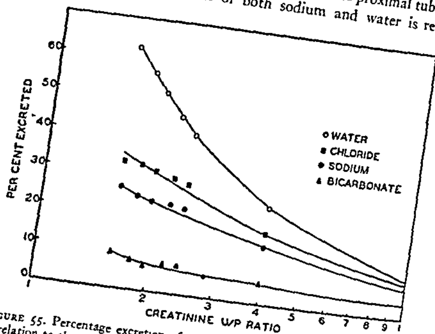


FIGURE 55. Percentage excretion of water, chloride, sodium, and bicarbonate in relation to the creatinine U/P ratio in a dog during osmotic (mannitol) diuresis. (Wesson and Anslow [1171])

sorbed. Wesson, Anslow, and Smith [1171,1173] have shown in the dog that, during osmotic diuresis induced by the intravenous infusion of hypertonic mannitol solutions, as much as 65 per cent of the water of the glomerular filtrate may be excreted in the urine at a time when only 13 to 27 per cent of the filtered sodium is excreted (fig. 55). Under the conditions of these experiments, the flow of urine is so great that any changes in composition of the urine effected by the distal tubule are relatively minor in magnitude, and the composition of the bladder urine can be taken to represent the composition of the tubular urine at the end of the thin limb.

The fact that much less sodium than water is swept out by osmotic diuresis shows, first, that the reabsorption of sodium in the proximal tubule is operationally independent of the reabsorption of water, and second, that sodium reabsorption is an active process rather than a process involving passive diffusion of sodium along with whatever water is reabsorbed. That sodium reabsorption is an active process is further demonstrated by the fact that sodium continues to be reabsorbed against a concentration gradient between urine and plasma of as much as 60 mEq/liter or more, so that the nominal sodium content of the reabsorbate (if all the reabsorbed sodium were dissolved in all the reabsorbed water) actually exceeds that of the plasma by 50 per cent or more.

Since the osmotic pressure of the urine closely approaches the osmotic pressure of the plasma during osmotic diuresis or deviates from it by being only slightly hypotonic, the authors conclude that the proximal reabsorbate is in the net isosmotic with the plasma.* The simplest explanation is that, as sodium and other constituents of the proximal tubular urine are reabsorbed, water diffuses back through the proximal tubule or thin limb to maintain an osmotic U/P ratio close to 1.0.

That osmotic diuresis causes decreased reabsorption of chloride has also been demonstrated by others. Schou[1739] infused hypertonic sodium sulphate in anesthetized (urethane) rabbits, obtaining urine flows of 15 to 17 cc/min and creatinine U/P ratios of 1.5 or less, the lowest recorded figure being 1.2.† At a creatinine U/P ratio of 1.4 to 1.5, well over 50 per cent of the filtered chloride was excreted. Cisek and Holmes[281] have shown that chloride excretion increases *pari passu* with diuresis in the dog during the continuous intravenous administration of

* Correctly, one should refer again to the renal interstitial fluid rather than plasma, but for brevity we shall consider the interstitial fluid as invariably isosmotic with plasma.

† Incidentally, it may be noted that there was marked increase in creatinine clearance and renal blood flow (as measured by a Rein thermostromuhr) in Schou's experiments, and a close correlation was observable between arterial pressure, renal blood flow, and filtration rate. He calculates that the filtration fraction reached values exceeding 50 per cent, but in no case did the oncotic pressure of the postglomerular plasma exceed 66 per cent of the mean arterial pressure, i.e. a glomerular pressure of 66 per cent of the arterial pressure is adequate to effect the filtration of large quantities of fluid.

hypertonic sucrose, glucose, sorbitol, and urea,* the total chloride excreted being unrelated to the nature of the diuretic. They found that reabsorption of chloride is minimal at the peak of diuresis and is uninfluenced by pituitrin or desoxycorticosterone. Brodsky and Rapoport [266] have shown that osmotic diuresis in man, effected by glucose or mannitol, sweeps considerable sodium and chloride into the urine, *the effect again being unrelated to the nature of the osmotic diuretic.* Relman, Goodyer, and Peterson [1694] have shown that mannitol and glucose diuresis, induced simultaneously with copious water diuresis, increases sodium and chloride excretion. *The simplest interpretation here* is that osmotic diuresis sweeps sodium out of the proximal tubule faster than the distal tubule can handle it; this sodium appears in the urine irrespective of the rate of distal water reabsorption.

Wesson and Anslow [2171] attribute the decreased reabsorption of sodium during osmotic diuresis to dilution of sodium in the proximal tubule urine; as osmotic diuresis increases in magnitude, the retardation of passive water reabsorption effected by the osmotic diuretic lowers the concentration of sodium in the proximal urine and increases the concentration gradient between urine and plasma against which sodium reabsorption is occurring to a critical value, and thereby retards the reabsorptive process. They believe that, in any one experiment, this concentration difference approaches a critical value, despite marked variations in the absolute plasma and urine sodium concentrations, and that this critical value ranges in various experiments from 60 to 90 mEq/liter. The unreabsorbed sodium in turn contributes by its own osmotic action to retarding water reabsorption,† thus further promoting the excretion of water because, no matter what the proportions of sodium and mannitol in the urine, the latter remains isosmotic with the plasma.

The fact that a concentration gradient exerts a limiting action upon proximal sodium reabsorption is in marked contrast to the absence of such an effect in the distal system, where all except the

* The effect of urea appears to be comparable to that of other diuretics, if the load is large enough to establish an equal diuresis.

† The authors suggest that unreabsorbed urea may, by its osmotic action, retard the proximal reabsorption of water and contribute to the circumstance that only 85 per cent of the filtered sodium and water are normally reabsorbed in the proximal tubule

last trace of sodium may be removed from the urine. They infer that, in the proximal tubule, large quantities of sodium are normally reabsorbed against a small concentration gradient, a circumstance which permits the proximal tubule to reduce the gross bulk of the abundant glomerular filtrate and to concentrate, within certain osmotic limits, the waste products therein destined for excretion. In the distal segment, small quantities of sodium are reabsorbed against a much larger concentration gradient (as in the case of the proximal reabsorption of glucose), but from a much smaller quantity of fluid.

The fact that, by all the evidence, the urine delivered from the thin limb to the distal tubule * is isosmotic with plasma demands acceptance of the belief that some fraction of filtered sodium normally remains in the tubular urine at the end of the thin limb and hence is available for reabsorption by the distal tubule.† The size of this fraction depends upon the relative amount of sodium reabsorbed proximally. If we accept, from the evidence cited in the previous chapter, that about seven-eighths of the water of the filtrate is reabsorbed proximally and that one-eighth is available to the distal tubule for reabsorption, then we must accept that one-eighth of the sodium is also available for distal reabsorption.‡

So long as the fraction of sodium and water reabsorbed proximally remains large and fairly constant, changes in distal reabsorption will have but little effect upon the total reabsorption of either constituent. Two noteworthy consequences issue directly from this fact. As seen in the equation

$$(1) \qquad P_{Na}C_F = T_{Na} + U_{Na}V$$

* The use of the term distal tubule here and elsewhere does not exclude some sodium and water reabsorption by the collecting ducts.

† That nearly complete reabsorption of chloride can occur in the proximal tubule is shown by the chloride-free urine of the sculpin,[444] but that the U/P ratio of sodium is significantly below 1.0 can only be inferred from this fact In any case, the urine is isosmotic with the plasma in the marine fishes, which [illegible]

‡ The calculation neglects the osmotic pressure of urea and other less important solutes

the absolute amounts of both sodium and water reabsorbed will increase or decrease almost in direct proportion to the filtration rate, so long as $U_{Na}V$ is small in comparison with $P_{Na}C_F$, as it always is under normal conditions. Indeed $P_{Na}C_F$ and T_{Na} are normally so nearly equal that T_{Na} appears to vary in direct proportion to $P_{Na}C_F$.

Second, if we divide (1) by C_F,

(2)

$$P_{Na} = \frac{T_{Na}}{C_F} + \frac{U_{Na}V}{C_F}$$

and write $C_F = T_{H_2O} + V$

(3)

$$P_{Na} = \frac{T_{Na}}{T_{H_2O} + V} + \frac{U_{Na}V}{C_F}$$

i.e. the nominal concentration of sodium in the total reabsorbate T_{H_2O} will deviate from P_{Na} only in so far as U_{Na} or V is significantly large. Hence, in the overall operation of the kidneys, the composition of the plasma will undergo change as a result of urine excretion only in so far as V is significantly large and U_{Na} deviates from P_{Na}, which is to say, only in so far as sodium or water is preferentially excreted in the urine. This is, of course, self-evident, and yet failure to recognize the tautological pitfalls of equation (1) sometimes leads to semasiologic difficulties.*

With the proximal reabsorption of sodium an active process and that of water a passive process, one would expect the proximal tubular urine to be, at times at least, slightly hypotonic to the blood. Walker, Bott, Oliver, and MacDowell[2131] obtained a hypotonic urine from the proximal tubule of the rat in only 2 out of 21 instances, but their observations were made on unilaterally nephrectomized animals which were generally loaded with sucrose or saline, circumstances which might alter the conditions of proximal reabsorption. It is conceivable that, under some conditions, the proximal urine may be distinctly hypotonic. If such is the case, the present view affords an attractive explanation of the function of the thin segment in the loop of Henle. The older idea, that because this segment occurs only in the Classes (birds and mammals) where ADH promotes water reabsorption it is itself the locus of the formation of a concentrated urine and of osmotic work, has

* The R/P ratio of Hare *et al.*;[917] figures 2 and 3 of Mokotoff *et al*[1440] on sodium reabsorption in patients in heart failure, the increased 'sodium reabsorption' reported in infants by Dean and McCance,[434] the correlation between $U_{Na}V$ and the 'tubular rejection fraction' of Green *et al.*[848]

never had strong appeal because the low epithelium of the thin limb does not, by contrast with the cuboidal cells of the distal tubule, seem cytologically constituted for such a function.* Perhaps the strongest argument against the formation of hypertonic urine in the thin segment is the fact that protein casts are never *found in this segment; casts first form in the ascending limb of the* distal tubule, with increasing precipitation in the distal convoluted tubules and collecting ducts In so far as cast formation is related to increasing concentration of protein, this circumstance indicates further water reabsorption in the distal system, which could scarcely be possible if the urine in the thin segment were already hypertonic to the plasma.

The present interpretation would be that the thin limb serves to promote osmotic equilibration by passive diffusion of water between tubular urine and plasma after the bulk of the sodium, etc., has been reabsorbed proximally.† Wesson, Anslow, and Smith [2173] accept the evolution of the thin segment as being related to the activity of ADH in promoting facultative water reabsorption (which they refer specifically to the distal tubule) and the capacity to excrete a hypertonic urine, but they see in the thin limb only an accessory adaptation facilitating the reduction to a minimum of the water load delivered to the distal tubule before final water and sodium reabsorption are effected. To deliver a variable excess of fluid having a variable osmotic pressure to this terminal segment would conceivably be disadvantageous to its precise operations in the critical retention of sodium and water, especially if either of these distal functions is itself limited by a critical rate

* [illegible] the present time.

† Shannon [illegible] supposed, incorrectly we now believe, that all the sodium was reabsorbed in the proximal system and that a very dilute urine, equivalent to that excreted during water diuresis, was delivered to the distal tubule. The present evidence appears to controvert this view.

Mudge, Foulks, and Gilman [1488] have carried out similar studies of extreme osmotic diuresis in anesthetized (pentobarbital) dogs, using 50 per cent urea solutions instead of mannitol. Water balance was maintained by infusing sodium chloride solution at a rate commensurate with urine flow. These investigators confirm that at high rates of flow the urine becomes approximately isosmotic with the blood, indicating that under these conditions the distal system is incapable of altering the composition of the proximal urine significantly. The tubular reabsorbate is isosmotic and, since only small amounts of urea are reabsorbed, sodium salts provide the major osmotic constituent of the reabsorbate. Since urea contributes largely to the osmotic pressure of the tubular urine, it follows that the sodium concentration of the reabsorbate is greatly in excess of that in both the tubular urine and plasma. The existence of this sodium concentration gradient between the tubular urine and reabsorbate reaffirms the evidence that the proximal reabsorption of sodium is an active process. The authors accept that water is reabsorbed by passive diffusion to maintain the proximal osmotic U/P ratio at 1.0. In prolonged experiments the urine may become hypotonic to the plasma, as indicated by rough calculations from sodium chloride and urea concentrations The authors believe this reflects circumstances under which sodium and other osmotically active agents are reabsorbed more rapidly than water.

Where Wesson and Anslow [2171] believed that the proximal reabsorption of sodium was retarded by a limiting concentration difference between plasma and proximal urine of 60 to 90 mEq/liter (the figure varying in different experiments), Mudge *et al.* found that this concentration difference showed no apparent upper limit, ranging from 0 to 100 mEq/liter as diuresis increased, and varied widely in single experiments and from animal to animal. This concentration difference varies inversely with the filtration rate, indicating that, with lowered sodium loads, more complete reabsorption of sodium occurs even in the presence of isosmotic urine. The authors conclude that decreased sodium reabsorption occurs because of the continuous decrease in sodium concentration as each increment of the glomerular filtrate is reabsorbed along the prox-

imal tubule, a condition which only applies in the presence of an osmotic diuretic.

The administration of a mercurial diuretic at the height of urea diuresis further decreased the reabsorption of sodium, but did not alter the concentration difference between tubular urine and reabsorbate, indicating that mercurial diuretics decrease the functional capacity of the proximal tubule cells to transfer sodium without altering the fundamental mechanism of reabsorption.

Incidentally, Mudge *et al.* showed that osmotic diuresis does not cause the excretion of glucose even when 53 per cent of the filtrate is excreted in the urine, nor does it accelerate the excretion of bicarbonate or of phosphate if the plasma phosphate concentration does not increase. The reabsorption of these substances proceeds independently of the reabsorption of sodium and water.

TUBULAR REABSORPTIVE ACTIVITY

In any study of sodium excretion it must be recognized that the reabsorptive activity of the tubule (proximal or distal) may change in consequence of changes in the intrinsic activity of the tubule cells, of changes in the secretion of ADH or adrenal cortical hormones (ch. XII), or for other as yet unidentified reasons. Such changes in reabsorptive activity are commonly assumed to be present both in non-renal and renal disease but their evaluation at the present time presents many difficulties. Analysis of the problem can best be approached by reducing the number of variables to a minimum. It is known that the administration of isotonic saline or Locke's solution to the dog increases the filtration rate, presumably an effect related to the expansion of the extracellular fluid. Wesson, Anslow, Raisz, Bolomey, and Ladd [2111] have utilized the increase in filtration rate induced in this manner to examine the question of variability in sodium reabsorption. After the infusion of either saline or Locke's solution, the urine may have a diverse composition during various phases of the resulting diuresis, and protracted diuresis may therefore lead to significant and variable changes in plasma composition. To offset this factor, Wesson and his coworkers determined the urine pattern in preliminary tests, and then in subsequent experiments continuously infused

the animal at such a rate and with fluid of such a composition as to avoid any changes in the plasma electrolyte pattern, thus maintaining an expansion of extracellular fluid of 25 to 50 per cent for

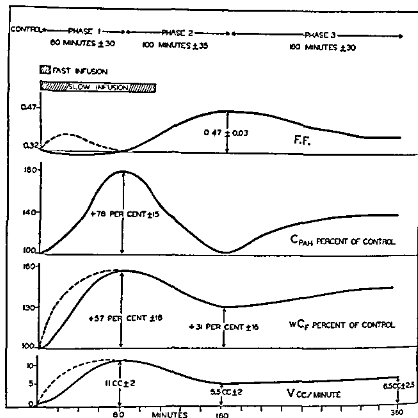


FIGURE 56. Average values for urine flow, filtration rate of water (wC_F), renal plasma flow, and filtration fraction following expansion of the extracellular fluid volume in 18 experiments on 6 normal dogs Numbers are means and ± mean deviations from the mean. *Before averaging the individual curves, the time* scales of the experiments on each animal were adjusted so that their inflections coincide with the average inflection times for all experiments (Wesson, Anslow, Raisz, Bolomey, and Ladd [2172])

6 to 8 hr. without change in composition, at least so far as the major electrolytes are concerned. Pitressin was also infused (20 milliunits/hr.) to promote to a maximal extent the reabsorption of water effected by this hormone.

These experiments reveal that the response of the dog to a sustained expansion of the extracellular fluid may be divided into

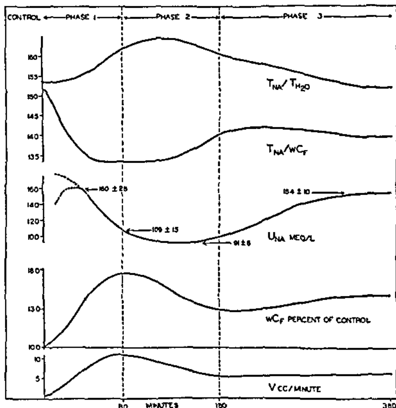


FIGURE 57 Urine sodium concentration, sodium reabsorption per unit of glo- [illegible]

Ladd [illegible])

three phases (fig. 56). In phase I, the filtration rate and renal plasma flow increase on the average by 57 and 76 per cent, respectively. In phase II, these functions decline to reach minimal values at about the same time, thereafter increasing again to

the animal at such a rate and with fluid of such a composition as to avoid any changes in the plasma electrolyte pattern, thus maintaining an expansion of extracellular fluid of 25 to 50 per cent for

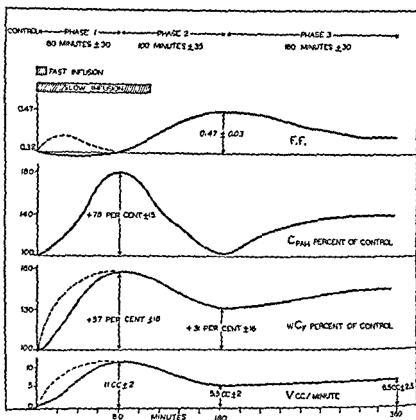


FIGURE 56. Average values for urine flow, filtration rate of water (wC_F), renal plasma flow, and filtration fraction following expansion of the extracellular fluid volume in 18 experiments on 6 normal dogs. Numbers are means and ± mean deviations from the mean. Before averaging the individual curves, the time scales of the experiments on each animal were adjusted so that their inflections coincide with the average inflection times for all experiments. (Wesson, Anslow, Raisz, Bolomey, and Ladd [1172])

6 to 8 hr. without change in composition, at least so far as the major electrolytes are concerned. Pitressin was also infused (20 milliunits/hr.) to promote to a maximal extent the reabsorption of water effected by this hormone.

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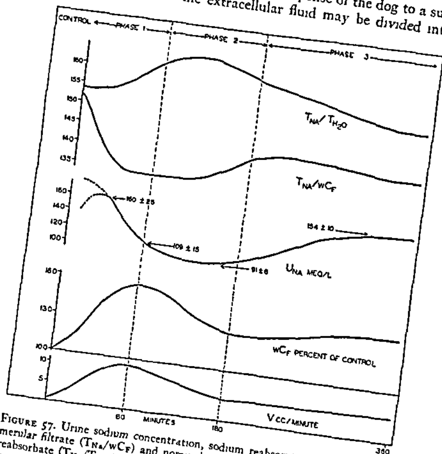


FIGURE 57. Urine sodium concentration, sodium reabsorption per unit of glomerular filtrate (T_{Na}/wC_F) and nominal concentration of sodium in the total reabsorbate (T_{Na}/T_{H_2O}) calculated from the mean values for the 6 longest experiments by the same procedure as the curves in figure 58 Urine flow and filtration rate are repeated from figure 56 for comparison Numbers are means and mean deviations from the mean (Wesson, Anslow, Raisz, Bolomey, and Ladd [2172])

three phases (fig. 56). In phase I, the filtration rate and renal plasma flow increase on the average by 57 and 76 per cent, respectively. In phase II, these functions decline to reach minimal values at about the same time, thereafter increasing again to

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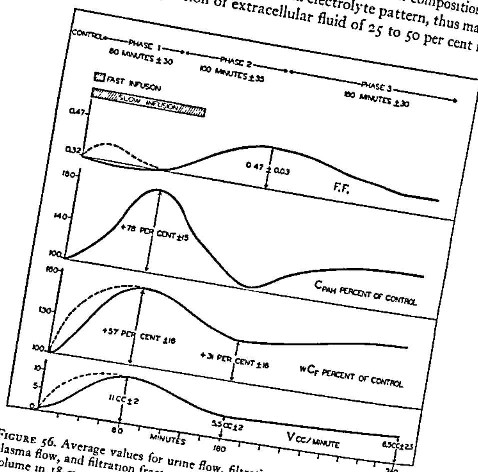


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6 to 8 hr. without change in composition, at least so far as the major electrolytes are concerned. Pitressin was also infused (20 milliunits/hr.) to promote to a maximal extent the reabsorption of water effected by this hormone.

These experiments, though complicated in design, show that mere expansion of the extracellular fluid, accompanied at least by

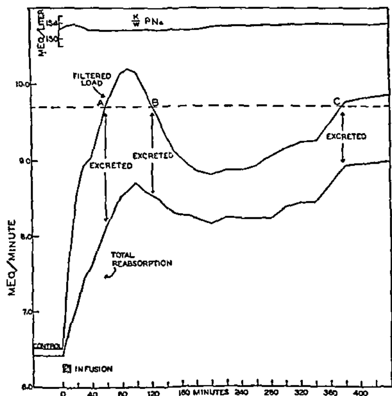


FIGURE 58 The filtered load of sodium ($k/wP_{Na} \times wC_F$) and rate of total sodium reabsorption in 2 dogs (2 experiments per dog) following fast infusion of Locke's solution The interval between load and reabsorption measures the

no changes in plasma electrolyte composition, increases the filtration rate and renal plasma flow, and the specific activity of the renal tubules in the reabsorption of both sodium and water at a constant filtered load of each. They reveal the difficulty of interpret-

fairly steady, supernormal values in phase III. These changes in filtration rate and renal blood flow were not related to blood pressure changes or dilution of plasma protein but, apparently, to expansion of the extracellular fluid volume as a whole or some part thereof.

The initial increase in filtration in phase I, figure 56, is accompanied by a marked increase in sodium excretion, which, the authors believe, is directly attributable to the increased load of sodium delivered to the tubules, since P_{Na} has remained constant.

In view of the general proportionality between the filtration rate and sodium reabsorption in the proximal system, there is no simple way in which one can express the reabsorptive activity of the kidneys for sodium when the filtration rate is changing. The absolute quantity reabsorbed, T_{Na}, is an unanalyzed function of the filtered load, $kP_{Na}C_F$, and, for this reason and because of possible (and here demonstrated) changes in water reabsorption mediated without relation to sodium reabsorption, the ratios T_{Na}/T_{H_2O} and T_{Na}/wC_F (fig. 57) afford no immediately useful information. Therefore, the only method of analysis now available is to compare T_{Na} under identical conditions of P_{Na} and C_F, and hence of the filtered load, $kP_{Na}C_F$. This can be done in these experiments at the points A, B, and C in figure 58, where the above-mentioned terms are constant. The data reveal that, at an identical load at these 3 points, T_{Na} averaged 8.12, 8.55, and 8.88 mEq/min.; i.e. tubular reabsorption increased by about 10 per cent. This increase, though slight in absolute terms, is sufficient at the existing filtered load of 9.70 mEq/min. to reduce the rate of excretion by one-half, i.e. from 1.58 to 0.84 mEq/min. The experiments throw no light on whether this increased reabsorption is attributable to the proximal or distal system, or on how it is effected.

During phase II, despite the continuous administration of pitressin in physiological doses, water reabsorption falls behind sodium reabsorption and the urine is for a time slightly hypotonic (fig. 57); this hypotonic state is followed by a hypertonic state in phase III. The data demonstrate that some factor other than ADH influences water reabsorption.

gard to the role of the osmotic pressure of the plasma in controlling sodium excretion Their argument, however, is based in part upon the assertion that, during osmotic diuresis caused by sodium sulphate and urea, chloride excretion is not increased, which is contrary to the evidence cited above. Nor is there *a priori* warrant for the statement that, if the action of mannitol and glucose were intratubular, the excretion of phosphate and potassium should also be increased; the mechanism of reabsorption of these substances, like that for glucose, is independent of the sodium mechanism. The arguments presented by the authors are inadequate to refute the intratubular locus of the action of osmotic diuresis in reducing sodium reabsorption.

Green, Bridges, Johnson, Lehman, Gray, and Field [849] report renal clearance and sodium excretion data on 60 hospital patients, all of whom had renal disease as judged by the filtration rate (41.5 ± 16 5 cc) and PAH clearance (228 ± 95 cc) The patients were chosen in order to afford a wide range of filtration rates. Ten were maintained on diets containing approximately 2 gm of salt per day. Mannitol was used to measure the filtration rate and was presumably administered in a salt-free solution. The authors examine particularly the per cent of filtered sodium which is excreted, which they call the tubular rejection fraction, TRF_{Na}. The total rate of sodium and water excretion during the experimental periods was much larger than was to be expected from the salt intake because of the clearance procedure. Since mannitol diuresis had substantially increased sodium and water excretion, the former to 33 gm sodium chloride per 1 73 sq m per day, the latter to 6.65 liters, sodium excretion under the conditions of the experiments has little bearing on the normal control of sodium excretion As the authors point out, in the presence of low filtration rates the per cent of filtered sodium excreted increases correspondingly, as must be the case if subjects with low filtration rates (essential hypertension, etc.) continue to maintain a constant plasma concentration on a normal salt intake The authors note that there is a high correlation between the rate of sodium excretion and the per cent of filtered sodium excreted, especially where $P_{Na}C_F$ is relatively constant This correlation is a tautological consequence of the fact that, where $P_{Na}C_F$ is constant, the ratio $U_{Na}V/TRF_{Na}$ is fixed thereby, and the demonstrated correlation merely reflects the narrow range of variation of P_{Na} and C_F in the subjects studied.

DISTAL REABSORPTION OF SODIUM AND WATER

Very little is known about sodium and water reabsorption distally. It cannot even be said to what extent these processes are restricted

ing changes in renal function in acute experiments where several variables are changing rapidly and simultaneously.

Selkurt, Hall, and Spencer [1825] have found that, when the filtration rate is reduced in one kidney of the anesthetized (pentobarbital) dog by reduction of local arterial pressure, moderate reduction of the filtration rate, to 63 per cent of the control value, leads to the rapid decline and cessation of sodium excretion Reabsorption is complete when the filtered load falls below 3.9 mM/min. per kidney (average weight 42 gm)

Green and Farah [850] examined sodium excretion in anesthetized (dial-urethane) dogs which were infused at a constant rate with strong sodium chloride solutions. Increase in the rate of sodium excretion necessarily reflected an increase in the 'tubular rejection fraction' (fraction of filtered load which was excreted), since, under the conditions of the experiment, $U_{Na}V$ varied through a much wider range than $P_{Na}C_F$ Water excretion paralleled that of sodium. The infusion of sodium chloride solutions did not produce consistent changes in the filtration rate in their experiments In 5 animals, infusion of the test solution was followed by a decrease in filtration rate, although sodium excretion increased, and in no instance did the greatest output occur during the period of maximal filtration The renal plasma flow consistently increased, but this increase did not invariably coincide with increased sodium excretion. No consistent relation was established between sodium excretion and plasma sodium concentration, sodium balance or sodium space (assuming only extracellular distribution equal to P_{Na}), water gain or loss, or hematocrit. The authors conclude that increased sodium intake influenced sodium excretion primarily by establishing an osmotic pressure difference between extra- and intracellular fluids, and that the major determinant in sodium regulation is not the preservation of sodium balance but the maintenance of osmotic homeostasis. The conclusion may be correct, but the data do not appear to establish the point experimentally The conclusion is based largely upon the calculation that the net change in sodium space was uniformly greater than the net water retention, indicating that water had been withdrawn from the tissues The calculation is suspect in the absence of evidence that changes in plasma sodium concentration were not reflected by changes in intracellular concentration and by the use of a single injection of mannitol to measure extracellular fluid volume, a method which is unreliable for this purpose.[1808, 1809]

Seldin and Tarail [1819] have arrived at a similar conclusion with re-

tion may be or under what circumstances it actually limits the reabsorption of water is not known. If physiologically significant, this maximal rate would only be attained under the influence of ADH, $T^d_{H_2O}$ falling below the maximal value and perhaps to zero in the absence of activation by this hormone.

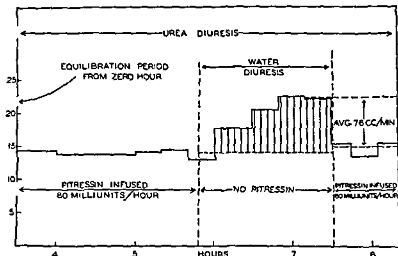


FIGURE 59 Facultative water excretion in a hydrated dog during osmotic (urea) diuresis After an equilibration period of some 6 hr (demonstrated by previous experiments to be necessary to obtain stable conditions with respect to sodium reabsorption), pitressin was withdrawn from the infusion, permitting the facultative water to be excreted in the urine.

Reasons are given in the text for believing that the water which must be abstracted from the urine (ΔV) during this diuresis in order to make it isosmotic with the plasma is quantitatively related to sodium reabsorption in the distal tubule Since the magnitude of ΔV is roughly constant at all levels of osmotic diuresis, this indicates that a constant quantity of sodium (T^d_{Na}) is reabsorbed distally under the conditions of the experiments (Wesson and Anslow, pers com)

Some intimations on the possible relations of distal sodium and water reabsorption have been sought by Wesson and Anslow (pers. com.) by examining the effects of pitressin on urine flow, with and without osmotic (urea) diuresis, the latter serving to increase the load of water and electrolyte delivered to the distal system. Here, as elsewhere, it is assumed, since there is no evidence to the contrary, that no water is excreted by any segment of the renal tu-

to the distal tubule or are carried on in the collecting ducts. The data from micropuncture studies indicate that sodium reabsorption occurs in the former but they do not exclude the latter. That water reabsorption may occur in the collecting ducts is indicated but not proved by the formation of casts, as pointed out above.

It has been noted that systems involving tubular transport have, with few exceptions, been demonstrated to be limited by maximal rates, or, at least, by rates which do not change beyond the limits of experimental error with increasing load, once the load has exceeded some critical value. In general, these maximal rates (Tm) of tubular transport are at least roughly reproducible in a particular individual under basal conditions. That the distal reabsorption of sodium is an active process is indicated by the fact that sodium may be abstracted from the urine to the point where the urine is practically sodium-free. Indeed, without marked reduction in filtration rate, a normal subject will maintain himself in sodium balance on as little salt as 0.5 gm/day and, for short periods at least, the urine may be almost devoid of an analytical trace of sodium.

Rats maintained on a low chloride diet (0.5 to 1.2 mg as compared to a control excretion of 110 to 170 mg. of chloride per day), for periods of up to 15 weeks, show no striking outward signs of deficiency, although they gain less weight and eat more food per gm. of body weight than do controls. In such animals, whole blood chloride is reduced (252 mg/100 cc. as compared with 295 mg/100 cc. in controls) and bicarbonate is increased (72.3 as compared with 57.7 cc/100 cc. in controls).[381]

These considerations lead us to anticipate that distal reabsorption of sodium (T^d_{Na}) must be limited by a maximal rate (Tm^d_{Na}), as suggested by Wesson, Anslow, and Smith.[2173] How sharp this limitation may be and under what circumstances it actually limits the distal reabsorption of sodium remains to be determined.

Distal reabsorption of water, unlike proximal reabsorption, also appears at first sight to be an active process, inasmuch as water is here abstracted against the osmotic pressure of the urinary solutes to yield a hypertonic urine, a process requiring the local expenditure of energy by the tubule cells. It is therefore to be anticipated in theory that distal water reabsorption ($T^d_{H_2O}$) is also limited by a maximal rate ($Tm^d_{H_2O}$), but, here again, how sharp this limita-

diuresis) in the same proportions as osmotically active substances and water are presented to the distal tubule by the thin limb; i.e.

$$T^d_{Na}/T^d_{H_2O} = P_{osm} \text{ or } T^d_{Na} = T^d_{H_2O}P_{osm}.$$

Since ΔV remains fairly constant in any one animal in the type of experiment shown in figure 59 both in water diuresis and during osmotic diuresis, when the load of sodium and water delivered to the distal tubule is increased, it would appear that facultative water reabsorption is correlated with a specific quantity of reabsorbed sodium, which we will here call T^d_{Na}, and that T^d_{Na} itself remains constant under these fairly extreme conditions.*

Since, during uncomplicated water diuresis, the urine is very dilute, this sodium must be reabsorbed at some point in the tubule which is impermeable to water; i.e. T^d_{Na} must represent absorption at some point below the thin limb (in the distal system). Hence the facultative reabsorption of water ($T^d_{H_2O}$) (and the action of ADH) must likewise be assigned to the distal system, coexistent with or lower down the nephron than T^d_{Na}.

Distal water reabsorption may not, however, be limited to that which appears in the urine during a water diuresis when this is superimposed upon osmotic diuresis, as in figure 59, because, independently of distal sodium reabsorption, an additional quantity of water ($T^x_{H_2O}$) may be abstracted from an isotonic urine to yield a hypertonic urine. The magnitude of this process, which is given by the quantity of water required to dilute the hypertonic urine formed during maximal osmotic diuresis back to the osmotic pressure of the plasma, is small relative to ΔV during water diuresis; consequently, as the distal load of water increases during osmotic diuresis (and under maximal ADH activation), the osmotic U/P ratio approaches 1.0. It is conceivable that $T^d_{H_2O}$ and $T^x_{H_2O}$ represent a unitary process located at one region of the distal system, or $T^x_{H_2O}$ may represent an additional process occurring farther down the nephron than $T^d_{H_2O}$ (The latter appears to be the most attractive view.) Whether $T^x_{H_2O}$ is under facultative control by

* That sodium reabsorption may be decreased by the action of pitressin is well known (ch. x), whether this effect is on the proximal or distal system is as yet undetermined, but the natriuretic effect appears to amount to no more than some 10 per cent of T^d_{Na}

bule. Figure 59 represents an experiment in which a dog was hydrated with 85 cc/kg. of water orally at the zero hour, and pitressin was administered at the rate of 80 milliunits/hr. to prevent water diuresis. Simultaneously, osmotic diuresis was established by means of a priming injection of urea, the plasma urea concentration being kept constant by the reinfusion of the urine. Previous experiments have demonstrated that 4 hr. are required to establish a steady state with respect to urine volume and composition. After a control period extending from the fourth to the sixth hour, the pitressin infusion was withdrawn, permitting the urine flow to increase to the extent to which this hormone was promoting the reabsorption of water. During the ensuing water diuresis, the urine, which hitherto had been approximately isosmotic with the plasma, became hypotonic. On reinfusion of pitressin, the urine flow decreased and the osmotic pressure increased to their prediuretic levels.

In successive experiments, the urea load (or level of osmotic diuresis) was increased in order to increase the distal load of sodium and water. The observations on any one animal indicate that the osmotic magnitude of the water diuresis (ΔV) resulting from the withdrawal of pitressin during osmotic diuresis, regardless of the level of the latter, is approximately constant and equal to the water diuresis obtained in experiments carried out in the same way except for the omission of osmotic diuresis. Here ΔV represents the quantity of water which must be abstracted from the urine in order to make it isosmotic with the concurrent plasma.

Assuming (a) that the thin limb is permeable to water and that the urine delivered to the distal tubule is exactly isosmotic with the plasma during water diuresis (an assumption which remains to be established), a hypotonic urine such as is excreted during water diuresis requires that some osmotically active substance be reabsorbed by the distal tubule; excluding the back diffusion of urea, we may further assume (b) that the only substance reabsorbed here in significant quantities is sodium. It follows that the difference between the osmotic pressure of the plasma and of the diuretic urine reflects the quantity of sodium being reabsorbed during water diuresis. Or, conversely, facultative distal water reabsorption is related to distal sodium reabsorption (during water

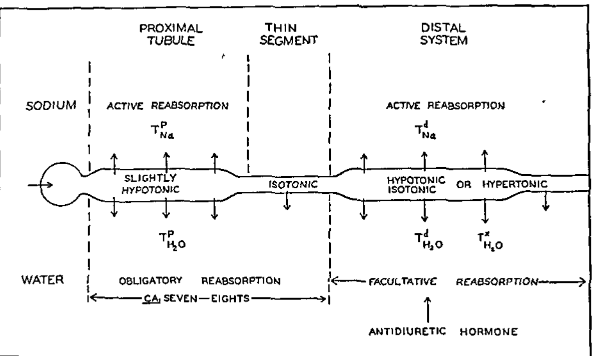


FIGURE 60 Schematic representation of sodium and water reabsorption.

ADH or is a continuous process which has little effect on the composition of the urine during water diuresis when $T^d_{H_2O}$ is small, is undetermined. In the first case, $T^x_{H_2O}$ does not appear in the calculation of T^d_{Na} since this computation is based upon P_{osm}, the theoretical osmotic pressure of the tubular urine before $T^x_{H_2O}$ was abstracted. In the second case, $T^d_{H_2O}$ is smaller than the water released by the absorption of T^d_{Na} by an amount equal to $T^x_{H_2O}$, and T^d_{Na} as calculated will be correspondingly less than the actual magnitude of distal sodium reabsorption.

In summary, it is clear that the facts are not available to answer with certainty several major questions relating to electrolyte reabsorption, and the following description is in some respects speculative. The theoretical formulation of Wesson, Anslow, and Smith,[2172] as modified by the studies cited above, represents as satisfactory a theory as any by which the known facts may be correlated.

The reabsorption of sodium is conceived as taking place in two stages (fig. 60): (1) a proximal process (T^p_{Na}) involving approximately four-fifths of the normal filtered load; (2) a distal process (T^d_{Na}) involving approximately one-fifth of the normal filtered load. To these we may add for completeness a small quantity (less than 1 or 2 per cent of the normal load) involved in independent ion [K^+, H^+, (NH_3^+?)] exchange processes. Water reabsorption involves a further process ($T^x_{H_2O}$) by which hypertonic urine is formed.

Proximal reabsorption is rapidly reduced when a sodium concentration gradient is developed between plasma and tubular urine. Normally, this concentration gradient remains small because of the rapid, passive reabsorption of water, but during osmotic diuresis the reabsorption of water is retarded and the sodium in the tubular urine is diluted, impeding its reabsorption. The fact that the proximal reabsorption of sodium is incomplete under normal filtered loads and that roughly 20 per cent is passed on to the distal system is possibly attributable to the circumstance that the diffusion of water does not proceed fast enough to maintain osmotic equilibration, and the resulting sodium concentration gradient acts to limit sodium reabsorption, this limitation being

tion as a bulk transfer mechanism, serving to reduce the gross volume of the glomerular filtrate, the distal process effects fine adjustment upon a small volume Since the ultimate excretion or retention of sodium depends upon this distal process, it is reasonable to suppose that this is the locus of such sodium reabsorption as is susceptible to hormonal control (corticosteroid, pituitary, etc.), and in this sense it is facultative, as in the case of water.

A small volume of isotonic fluid (of which about 10 per cent of the total osmotic pressure is attributable to urea and most of the rest to sodium salts) enters the distal tubule. Here the distal process reabsorbs sodium until the urine is sodium-free, or the distal reabsorptive capacity (T^d_{Na}) (conditioned in part by hormones) is exceeded. Such sodium as is reabsorbed distally liberates an osmotic moiety of water which, in the absence of ADH, contributes to the production of a hypotonic urine, the decrease in urine osmotic pressure being equivalent to the distal reabsorption of sodium.*

In the absence of ADH, the hypotonic urine left after the reabsorption of sodium continues into the bladder without further important changes In the presence of ADH, the facultative water reabsorptive process ($T^d_{H_2O}$) is activated. The water osmotically liberated by the reabsorption of sodium is now reabsorbed to produce an isosmotic urine. Further water reabsorption ($T^x_{H_2O}$) from the urine, which now has a small bulk, leads to the formation of a hypertonic urine, the limiting factor here being apparently the maximal osmotic U/P ratio. $T^x_{H_2O}$ is not only small but is apparently limited in rate, so that urine of maximal osmotic pressure is formed only at low urine flows. Whether $T^d_{H_2O}$ and $T^x_{H_2O}$ are referable to the same portion of the distal tubule, or whether $T^x_{H_2O}$ is referable to a lower portion of the nephron (collecting ducts?) than $T^d_{H_2O}$, is as yet undetermined

Changes in sodium excretion may be brought about in two ways: (1) by changes in the distal load of sodium effected by changes in the rate of filtration; (2) by changes in the rate of

* The theory up to this point would serve to explain the excretion of an os-ically dilute urine in those Classes which have only a proximal and distal ent in the nephron, and in which ADH is not active with respect to water sorption.

supplemented by the presence of osmotically active substances (urea, sulphate, etc.) in the urine, which retard water reabsorption.

In this view, the proximal tubule is always *maximally engaged* in sodium reabsorption within the limits imposed by the composition of the tubular urine at each point along the tubule. Elevation of the filtration rate will, however, by increasing the volume of fluid delivered to the tubule, serve to abolish concentration differences from whatever cause, so that the absolute rate of sodium reabsorption will tend to increase *pari passu* with the filtration rate. Conversely, a decrease in filtration rate exaggerates the proximal concentration gradient, so that the absolute rate of reabsorption will tend to decrease. Hence there is an approximate though not strict proportionality between filtration rate and proximal reabsorption. The absolute rate of reabsorption may be expected to approach an asymptote as the filtration rate increases and, conversely, with decreasing filtration rate, reabsorption may be expected to become much more complete, so that, at half the normal filtration rate, perhaps more than 90 per cent of the filtered sodium may be reabsorbed. The effect of changes in the sodium concentration in the glomerular filtrate upon proximal reabsorption may be conceived as qualitatively but not quantitatively similar to the effect of changes in filtration rate.* At low plasma sodium concentrations, it may be expected that a larger fraction of the filtered sodium will be reabsorbed proximally than at normal concentrations, and *vice versa*.

The thin segment is conceived as a region that is highly permeable to water, wherein the variably hypotonic proximal urine is brought to osmotic equilibrium with the plasma. If an isotonic urine issues from the thin limb, we must accept that sodium can be reabsorbed distally. This distal process is characterized by the facts that it is capable of extracting virtually the last trace of sodium from the urine, and that the magnitude of the reabsorptive process, when fully engaged, is much smaller than that of the proximal process. Whereas the proximal process appears to func-

* As a consequence of the probable difference in the response of the kidney to the two factors, volume and concentration, it is unrealistic to describe sodium excretion in terms of the total load, or the product of volume and concentration.

visions a pattern of glomerular-tubular balance in which both glomerular and tubular activity are variable, but through appropriate compensatory changes the system can maintain salt and water balance through a wide range of activity in either component.

The foregoing considerations lead us to speculate whether there exists in the body a mechanism by which expansion or contraction of the extracellular fluid tends automatically to increase or decrease the filtration rate, or otherwise influence the reabsorption of sodium. Some evidence on this point will be discussed in the following sections.

EFFECT OF SALINE UPON THE FILTRATION RATE IN THE DOG AND RAT

It has long been recognized that the administration of isotonic saline increases the filtration rate in the dog Schmitz [1193] observed increases of 27 to 89 per cent in the dog after the intravenous administration of quantities no larger than 100 to 150 cc., and Shannon [1881] utilized this phenomenon in his interpretation of how the diabetes insipidus dog maintains itself on salt and water balance on a low and high salt intake. The phenomenon is apparent in the studies of Hare, Hare, and Phillips [917] in both diabetes insipidus and normal dogs, and in those of Wesson, Anslow, and Smith,[2172] where its possible relation to the maintenance of normal salt and water balance was emphasized

Baldwin, Kahana, and Clarke [77] record that the infusion of 0.9 per cent saline at a rate of 1 to 3 cc/min. in 2 dogs increased the filtration rate from a mean of 67 8 cc (range 41.6 to 91.5) to the range of 80 9 to 94 8 cc, and the PAH clearance from a mean of 209 cc (range 124 to 295) to the range of 218 to 399 cc. Ten per cent saline (2 to 5 cc/min.) had even more marked effects on both functions The filtration fraction in both instances remained fairly constant

Green and Farah [850] did not observe an increase in filtration rate in dogs infused with 1 7 M sodium chloride, but this function nearly doubled in a dog infused with 0.147 M. Why the more concentrated solutions should be without effect on glomerular activity in their experiments is not clear.

(distal?) reabsorption under hormonal control. The maintenance of salt and water balance probably involves both factors. Expansion of the extracellular fluid without change in composition in respect to the important electrolytes is known to increase the filtration rate; this increased filtration first increases the distal load to a point of overloading T^d_{Na} (phase I, figs. 56–58) and more slowly (phase II) leads through unidentified mechanisms to an increase in T^d_{Na} itself, the latter causing decreased excretion at a constant load (see fig. 58). Both mechanisms are probably operative in maintaining the volume of the extracellular fluid and salt and water balance. Conversely, reduction of body fluids is known to decrease the filtration rate; this decreased filtration reduces the distal load of sodium to a level less than T^d_{Na}, leading to sodium retention. Reduction of extracellular fluid may also set in operation mechanisms that increase T^d_{Na}. Where the reduction in filtration rate is extreme, irrespective of slight variations in T^d_{Na}, it will lead to excessive retention of sodium. In any instance, loss or retention of sodium, operating through the osmotic pressure of the plasma and the supraopticohypophysial system, will lead to loss or retention of water until the homeostatic osmotic pressure of the plasma is restored. The slowness with which glomerular and tubular activities are adjusted in man would explain the slowness with which saline diuresis is initiated, and the relatively small increase in the filtration rate, together with the fact that the distal process operates upon only a fraction of the total filtrate, would explain the relatively small magnitude of the diuresis.

The present value of any theory in this field must be sought not in the completeness with which it encompasses all the facts, but in its agreement with most of them and in the extent to which it can guide or suggest further investigation to affirm or disprove it. The notable advantage of the present interpretation is that, by physiologically integrating the renal mechanism controlling the excretion of sodium, the supraopticohypophysial mechanism controlling the excretion of water, the glomerular apparatus controlling the filtration rate, and the action of the hormones of the adrenal cortex and neurohypophysis on the distal (?) system, one would have a system that would regulate not only the composition of the extracellular fluid but its volume as well. This theory en-

subject, who showed no increase in filtration rate, showed no increase in sodium or chloride excretion, while in a third there was no correlation between the filtration rate and the excretion of sodium. Sodium citrate was without effect upon the filtration rate, partly because of conversion to and preferential excretion of sodium as bicarbonate.

Among the variable factors involved in determining the response to saline in man (and possibly in the dog) is the previous history of the individual with respect to hydration. Ladd [1185] has found that if normal subjects are hydrated with 2000 cc. of tap water 9 to 11 hr before the administration of saline (3000 cc. of 0.9 per cent sodium chloride intravenously at 45 to 65 cc/min), they respond with a transient, paradoxical water diuresis, in that large quantities of dilute urine are excreted during the later part and shortly after saline administration At the peak of diuresis the U/P ratio of inulin or endogenous creatinine chromogen falls to the range of 5 to 8 (average 6 0). This seems to involve a water diuresis rather than a pure saline diuresis because the osmotic U/P ratio decreases to the range of 0 3 to 0 7 (average 0.4); whereas in saline diuresis, as observed in non-hydrated subjects, this ratio remains above 1 0 at the highest urine flows.

The preliminary dose of water, of course, produces a typical diuretic response, as revealed by chromogen U/P ratios of 6 to 9 and by the excretion within 4 hr. of some two-thirds of the administered water. One notable feature of this phenomenon is that it fails to occur in subjects hydrated with the same dose of water less than 7 or more than 14 hr. before the injection of saline. It appears that this period of hydration has left some trace or hysteresis effect in the body which transmutes a saline diuresis into a water diuresis. A second notable feature is that during the administration of saline the osmotic pressure of the plasma (as measured by freezing-point depression) increases; i.e. water diuresis occurs in the face of the signal stimulus which should induce maximal water reabsorption. This paradoxical diuresis may be prevented or arrested by the intravenous administration of pitressin in physiological doses and fails to occur after the intravenous administration of hypertonic saline (3000 cc of 1.2 per cent sodium chloride solution), indicating failure of response of a still active supra-

jects; in 6 instances the filtration rate decreased by 5 per cent or more. The results were no different in 4 patients who had been maintained for a week on a high salt diet. In only 6 instances did the PAH clearance increase after saline by more than 10 per cent (12, 16, 16, 20, 28, and 123 per cent). Hypertonic saline (500 cc. of 5 per cent salt solution) was slightly more effective but still unimpressive; the filtration rate increased in 3 instances (16, 19, and 98 per cent), remaining essentially unchanged in the other 3 (−2, +6 and 7 per cent); the PAH clearance increased in 5 instances (11, 22, 26, 39, and 90 per cent) and decreased in 1 (7 per cent).

In the face of the effectiveness of saline in increasing glomerular activity in the dog and rat, and in the face of the all but firmly established relationship between extracellular fluid volume and glomerular activity (with reference to glomerular-tubular balance and sodium excretion), these negative results are at least disquieting. They imply to the writer that glomerular activity in man is stabilized to a greater degree than in the other species studied, or that its regulation involves undiscerned factors which are of less importance in the other species. It is significant, as Crawford and Ludemann emphasize, that isotonic and hypertonic saline are retained in man for long periods, only some 25 per cent at best being excreted within three and a half hours, in contrast to the dog, in which, after the administration of isotonic saline, a return of 75 per cent or better within this period may be expected. The marked increase in filtration rate and rapid excretion of saline in the dog and the absence of such an increase and the sluggish excretion in man are doubtless causally related.

Crawford and Ludemann find no correlation between the changes in filtration rate and sodium excretion. In 7 out of 11 instances, the rate of sodium excretion increased after isotonic saline by more than 10 per cent (16 to 282 per cent) despite no change or a decrease in filtration rate. This circumstance can only reflect changes in the reabsorptive activity of the tubules Leaf, Couter, and Newburgh [1220] report that when a normal subject changed from a low to a high salt diet the filtration rate and endogenous creatinine chromogen clearance increased by about 33 per cent, and were accompanied by increased sodium excretion; a second

WATER RETENTION AND ITS EFFECTS ON SODIUM BALANCE

The fact that sodium retention in man leads to water retention is clearly demonstrated The question whether water retention leads directly to sodium retention is not so clearly answered. As noted in chapter x, chloride excretion increases abruptly during the transient polyuria and the onset of permanent polyuria in diabetes insipidus animals, but neurohypophysectomy appears to produce no specific change in the manner in which the kidney handles sodium, for permanently diabetic animals soon come back into normal sodium balance [1768,2245] In view of the trauma associated with the production of experimental diabetes insipidus, this transient excretion of chloride is difficult to interpret.

Short-term water diuresis experiments are equally difficult to interpret. Eggleton [879] found that, during water diuresis, chloride excretion decreased in 8 out of 9 subjects, the average decrease being 30 per cent, confirming earlier investigators cited by her During the diuresis induced by alcohol (which apparently inhibits ADH secretion) a similar decrease in chloride excretion occurred [888] Crutchfield and Wood [457] report that water diuresis usually decreased sodium excretion; however, the difference in the mean excretion of 41 patients selected without regard to the control output (330 8 mg/hr during diuresis as compared with 336 0 mg in the controls) is so slight that its significance is questionable The authors state that, if the control urine flow is 'low,' sodium excretion may be increased by diuresis, but their division of patients with respect to 'low' and 'adequate' urine flows is somewhat arbitrary Opposed to these reports are the data of Barclay, Cooke, Kenney, and Nutt,[82] which show no consistent pattern of chloride excretion during water diuresis. Kattus *et al*,[1093] in well-controlled but short-term (3 hr) experiments, noted that large variations in urine flow did not appreciably modify the pattern of sodium excretion, but inspection of their data reveals that water diuresis (during their control periods before exercise) was almost invariably accompanied by increased sodium excretion, never by decreased excretion.

It would seem that, if short-term water diuresis *per se* does affect sodium excretion, the effect is easily obscured by unrelated variations in sodium balance, filtration rate, and other factors The evidence as a whole can scarcely be said to support the belief that hydration of the body leads directly or indirectly to sodium retention.*

* The point assumes importance in view of the implicit assumption by several workers that increased excretion of ADH or other antidiuretic factors in

opticohypophysial system under conditions that normally activate it. Whatever the explanation, Ladd's observations may help to clarify some of the irregularities in the response of man to saline, as well as the fact that the diuretic response to water itself is quite variable.

The sluggishness of the human kidney in respect to its response to saline can be observed in other studies presenting no specific information on renal function. Stewart and Rourke [2008] report the administration of 0.9 per cent saline to the extent of 6.5 liters/day to postoperative patients expanded thiocyanate space by approximately 90 per cent and plasma volume by 60 per cent. The daily increments, however, become progressively smaller and by 3 to 5 days a maximal expansion was followed by a gradual subsidence. Increase in the quantity of plasma protein maintained a protein concentration at nearly 6 gm/100 cc. Similar quantities of 5 per cent glucose reduced the volume of the thiocyanate space, possibly, as the authors suggest, because of the failure of the kidneys to conserve sodium in the face of the (glucose and ?) water diuresis. Unfortunately, since these observations were made in postoperative patients, neither the accumulation data nor the apparent compensation of the body to repetitive administration can safely be transferred to normal subjects.

Perera and Blood [1889] have shown that normal subjects, when deprived of salt, undergo diuresis and loss of weight (*c.*1 kg) in 24 hr., while Grant and Reichsman [843] report that subjects taking 20 to 30 gm of salt per day with water *ad libitum* show within 48 hr. a similar gain in weight, the plasma volume, blood volume, venous pressure, and thiocyanate space also being increased.* Lyons, Jacobson, and Avery [1335] report an average weight gain of 1.9 kg. in 7 subjects taking 40 gm. of salt in 48 hr. In 6 of these the plasma volume increased by a mean of 15.6 per cent Sodium bicarbonate had a similar but significantly smaller effect on weight /

Eichelberger and Roma [890] report that, when hypotonic saline (77 mEq/liter) was infused in large volumes into dogs, the average urine excreted contained 90 mEq/liter of sodium and chloride, while the concentration in the retained fluid ranged from 60 to 76 mEq/liter. The resulting hemodilution leads to a movement of extra water into the muscles, liver, skin, erythrocytes, and brain.

* Hypertensive subjects do not show this abrupt change in weight,[1889] but weight loss is evident when they are kept on a low salt diet for longer periods.[335]

to interpret experiments on the effects of drugs and hormones on chloride excretion without further data.[1179, 1180 1181]

DIURNAL VARIATIONS IN GLOMERULAR ACTIVITY AND IN ELECTROLYTE AND WATER EXCRETION

It has long been known that there is a diurnal rhythm in water and electrolyte excretion in man [1379 1898, 1899] The urine volume and urinary sodium, potassium, and chloride excretion are substantially greater during the day than at night, the larger urine volume of the day being associated with a negative water balance counterbalanced at night by a positive water balance Only slight fluctuations are evident in urinary phosphate, sulphate, titratable acidity, and ammonia, although there is almost uniformly a larger excretion of all these solutes during the day than at night No significant shift in calcium and magnesium was observed The excretion of water and electrolytes reaches a maximum from 6·00 A.M. to 12 00 noon, declines in the afternoon, and falls off sharply at night to reach a minimum from 12:00 midnight to 6·00 A.M The specific gravity, attributable largely to the nitrogenous fraction, is highest at night because of decreased urine volume, in spite of the fact that the total amount of nitrogen excreted is slightly diminished Dehydration and fasting do not markedly affect this diurnal rhythm in sodium and water excretion, although fasting may reverse potassium excretion

The mechanism involved in maintaining this diurnal rhythm appears to be related to the sleeping and waking states rather than to changes in physical activity, although the influence of the latter has not been wholly excluded If the individual sleeps during the day and is active at night, the rhythm is reversed.[1833] Simpson [1899 1900] had earlier shown that the excretion of phosphate and chloride is lower during sleep than during the waking hours in fasting subjects resting in bed under circumstances which do not disturb phosphate metabolism. Short periods of sleep during the day caused a decrease in urine volume in only 1 out of 17 subjects, showing the persistent tendency of the diurnal rhythm.

The studies of Popper and Brod,[1645] and Brod [258] indicate that this diurnal rhythm is accompanied by a qualitatively parallel variation in filtration rate, as judged by the endogenous creatinine chromogen clearance, which increases during the morning and decreases at night, and particularly during sleep The rhythm is reversed in chronic congestive heart failure (ch. XXII)

Sirota, Baldwin, and Villarreal,[1904] using a constant intravenous low-speed infusion pump with a flexible plastic intravenous catheter, have

It is of interest that Eggleton [879] found that, in the same individuals, tea (560 cc.) increased chloride excretion by 150 per cent while water decreased it by 70 per cent. The diuretic response was itself 30 per cent greater with tea than with water. This may in part be related to an increase in filtration rate produced by caffeine, but more important is the fact that xanthine derivatives increase sodium excretion by specifically reducing tubular reabsorption (ch XXVII).

EXERCISE

Barclay and his coworkers [82] report that chloride excretion is consis ently reduced during exercise, and Sinclair-Smith, Kattus, Genest, an Newman [1902] have shown that mild exercise (walking 3 m.p.h. on a motor-driven treadmill) causes significant retention of sodium and chloride, independently of changes in filtration rate as measured by the endogenous creatinine or inulin clearance. The fraction of filtered sodium excreted was reduced by 17 to 65 per cent (average 63) of the value obtained during the control period, increased reabsorption persisting for an average of 37 min after the end of exercise. Standing quietly had a slight effect in promoting sodium and chloride retention Variable but typical antidiuresis was associated with exercise. The excretion of potassium and phosphate showed no predictable correlation with changes in sodium excretion Sodium retention is not related to loss of sodium in sweat or to elevation of blood lactic acid; the authors note that it may reflect changes in the secretion of the adrenal cortex or neurohypophysis.

De Muylder and his coworkers [499, 600, 601, 602, 603, 604, 605, 606] have reported sodium chloride and potassium clearances in rabbits, including observations after the injection of pitressin in small and large doses, and of isotonic saline and glucose, as well as observations of the effects of such injections and of the subcutaneous injection of hypertonic glucose on the inulin clearance and minimal inulin U/P ratio. They develop the theory that oliguria or anuria is the result of a reduced filtration rate, which is itself a compensatory reaction to increased oncotic pressure and hyponatremia. In view of the ease with which reflex oliguria can be established in the rabbit, uncertainties with respect to variations in glomerular activity in relation to hydration and the complications presented by osmotic diuresis, these experiments are difficult to interpret. The complexities presented in the excretion of sodium make it difficult

hepatic cirrhosis, cardiac failure, etc , leads first to water retention and then to sodium retention and the production of edema The assumption seems at present to have no evidential foundation

Baldwin, Villarreal, Sirota, Schreiner, and Wesson (pers. com.) found that in 4 of the subjects above in whom the N/D inulin clearance ratios were 1.02, 1.13, 0.97, and 0.94, respectively, the N/D ratios for sodium excretion were 0.77, 0.79, 0.71, and 0.59. In a fifth, in whom the N/D inulin clearance ratio was 0.97, the N/D sodium ratio was 1.81. Despite constancy in the filtration rate, there appears to be a definite increase in sodium reabsorption at night, except in the 1 patient noted.

CONTINUOUS DIURESIS

Coon, Noojin, and Pfeiffer[401] gave 100 to 300 cc/kg of fluid orally to dogs in doses of 50 cc/kg every half hour. The rate of onset of diuresis was largely independent of salt content but the maximal urine flow (8 c/min. in a 10 kg dog) was obtained with 0.4, 0.5, and 0.6 mg per ent of sodium chloride, lower urine flows being obtained with stronger (0.7, 0.9 per cent) and weaker (0.2 or 0.1 per cent) solutions; 0.2 per cent sodium chloride produced the least change in chloride balance, as shown by lack of cumulative action and minimal change in serum chlo-ride. They suggest that 0.5 per cent sodium chloride is most diuretic because it is more rapidly absorbed from the gastrointestinal tract than are more concentrated solutions, but once the fluid is absorbed the kid-ney cannot (?) excrete more than 0.2 per cent sodium chloride in diuretic quantities. This interpretation may be questioned in favor of differential effects on the filtration rate and on the several systems involved in the excretion of salt and water. Pfeiffer *et al*[1602] report the effects on diuresis in dogs of adding calcium, magnesium, and potassium to 0.45 per cent sodium chloride. Their results must await further knowledge for interpretation.

Wolf[2258,2267] has shown that, when salt solutions of various concentrations are given intravenously to dogs at a rate of 2.3 cc/min., excretion of salt and water ultimately approaches a steady state which in most instances is reached by the seventh hour. Two concentrations of infusate yield a urine with about the same chloride/water ratio as the infusate, 170 mEq/liter (which Wolf calls the non-limiting isorrheic* concentration), and c 500 mEq/liter (which he calls the limiting isorrheic concentration). In similar studies on man, Wolf defines a third, or minimal, isorrheic concentration of c 40 mEq/liter, which presumably is also applicable to the dog. The non-limiting isorrheic concentration

* An isorrheic concentration is one at which, during a steady state, relative input of salt and water is equal to relative output of salt and water. The term was first used by Eggleton, Pappenheimer, and Winton[544] in their studies of the isolated kidney

followed the filtration rate and renal plasma flow throughout a 24 hr. period. The mean night to day (N/D) or sleeping/waking ratio for urine flow in 18 normal subjects was 0.83 ± 0.39, for inulin U/P ratio 1.40 ± 0.41, for inulin clearance 0.96 ± 0.07, for endogenous creatinine chromogen clearance 0.97 ± 0.06, and for PAH clearance 0.98 ± 0.06,

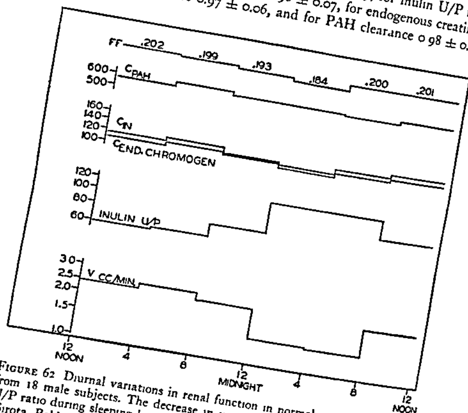


FIGURE 62 Diurnal variations in renal function in normal man. Average data from 18 male subjects. The decrease in urine flow and the increase in inulin U/P ratio during sleeping hours (12 P.M. to 8 A.M.) are statistically significant. (Sirota, Baldwin, and Villarreal [1904])

the data indicate a significant decrease in urine flow, a significant increase in tubular reabsorption of water, and a relatively constant filtration rate and renal plasma flow. However, during the 4 hr. period from 12.00 midnight to 4.00 A.M., corresponding to the period of deepest sleep, there was a slight but significant fall in filtration rate with no change in renal plasma flow (fig. 62). The decrease in urine flow at night is almost wholly attributable to increased tubular reabsorption of water. Simpson [1898] has shown that antidiuresis occurs even when the fluid intake at night equals that of the day.

body fluids, the experiments are not designed to throw any light upon the mechanisms involved.

Wolf[2258] reports that, when protracted water diuresis is maintained in man by repetitive drinking at rates varying from 6 to 10 cc/min, the rate of excretion of water comes ultimately to exceed the rate of intake by an average of 8 per cent. The total output, including insensible loss (0.7 cc/min.), may exceed intake by 15 to 25 per cent. During this maintained diuresis, the chloride concentration of the urine decreases to a minimum of *c* 34 mEq/liter, the rate of excretion leveling off at *c* 0.28 mEq/min. The reasons for continued chloride excretion are unknown, and no information is available relative to sodium balance, but the data are interpreted as showing that sustained water diuresis of sufficient magnitude has both a dehydrating and chloruretic effect.* Wolf finds that the chloride lost during diuresis, if referred to the excess water excretion plus water lost by insensible perspiration, has the proportion of about 170 mEq/liter, a figure identical with the non-limiting isorrheic concentration in dog and man, implying that the excess water is excreted because of the loss of chloride from the body. (This relationship breaks down when the water intake exceeds 10 cc/min., presumably because the kidneys are unable to excrete water as fast as it is ingested and the condition of a 'steady state' cannot be maintained.) One might infer that the addition of salt to the ingested fluid to the extent of 40 mEq/liter results in an equalization of the relative rates of salt and water intake and output (minimal isorrheic concentration), compensating for the disturbance in sodium balance occasioned by water diuresis.

Wolf and Ball[2261] have studied the 'steady states,' with respect to sodium and sulphate excretion, which are reached in the dog as a result of the prolonged infusion of various sodium sulphate solutions. They find the infusion of isotonic sodium sulphate (134 mM/kg. water at 4.1 cc/min.) leads ultimately to a urine flow close to the rate of infusion.

In the absence of more detailed knowledge of the effects of such solutions on glomerular and tubular activity, the data collected during sustained infusions throw no light on the fundamental renal operations or upon non-renal factors which may be important in controlling sodium excretion. The analysis of renal function must necessarily progress slowly, but it seems doubtful to the writer that it will be accelerated by the empirical approach.

*The dehydrating and chloruretic effects are not demonstrated at diuretic rates as low as 5 liters/day of water (3 cc/min.), as recommended for the treatment of cardiac edema.[1779]

of 170 mEq. presumably represents a fluid upon which, after prolonged infusion, the body performs no changes in its overall operations of salt and water conservation. This figure is not far from the isosmotic concentration of sodium chloride (0.945 gm/100 cc. of water, or 161 mEq/liter) and it is not clear whether or not the difference is significant.

At infusion concentrations above c.500 mEq/liter, relatively more water than salt is excreted, so that dehydration and salt retention occur. Such infusions are rapidly injurious, leading to intense thirst and sodium intoxication.* Between concentrations of 170 and 500 mEq/liter, the kidney operates to convert such fluid as is retained to a concentration of 170 mEq/liter by excreting more salt than water. This is essentially the 'threshold' plasma concentration (106 mEq/liter) described by Rehberg,[1659] at which water and salt were reabsorbed (and therefore excreted) in exactly the same proportions as they are present in plasma. Conversely, between 40 and 170 mEq/liter the kidney operates to convert the retained fluid to a concentration of 170 mEq/liter by excreting more water than salt. At 40 mEq/liter, the urine again has the same concentration as the infusate. This is virtually a state of water diuresis with salt loss which is perfectly compensated by the simultaneous excretion of infused salt, as described below. Below 40 mEq/liter, more water than salt is excreted—the response is that of simple water diuresis. For urea, the only isorrheic concentration is 35 mg/cc., which appears to reflect a maximal urinary concentration during the steady state of Wolf's experiments. Wolf[2259] has applied his overall balance studies to the excretion of potassium chloride, potassium bicarbonate, ammonium chloride, and sodium bicarbonate, and presented certain 'constants' which he believes to be physiologically significant. He has also presented a method of calculation of the osmotic changes in the extracellular fluid induced by varying loads of solute.[2259]

Wolf's non-limiting isorrheic concentration for sodium chloride (170 mEq/liter) is, as noted above, nearly identical in osmotic pressure with the plasma (161 mEq/liter). One might infer that, at this level, the complex mechanisms for conservation or rejection of water and salt are minimally activated, and with infusions of lesser concentrations the complex adjustments of the glomerular apparatus and of sodium and water reabsorption are operating to restore the plasma sodium concentration to this value. Although affording an interesting approach to the ultimate consequences of changing the volume and composition of the

* The value of 500 mEq/liter is not the maximal sodium chloride concentration of the urine, which reached 725 mEq/liter in some of Wolf's studies on the dog and 610 mEq/liter in those of Adolph on man.[27]

of the filtration rate (range 6.2 to 13 0), and the chloride U/P ratio fell from 2 or above down to exactly 1 0. Glucose excretion was only slightly increased. Although the author does not suggest this interpretation, the results are suggestive that cyanide may have a specific action on the distal tubule, blocking the distal reabsorption of sodium and water and the acidification of the urine by H^+ ion exchange; in the proximal tubule the only indicated action is the arrest of tubular excretion; the proximal reabsorption of glucose and of sodium appeared to be unimpaired.

HISTOCHEMICAL STUDIES OF CHLORIDE DISTRIBUTION

Several cytological and histochemical studies have been made of the distribution of chloride in the renal medulla and cortex by Feyel and Vieillefosse,[641] Glimstedt,[787] Ljungberg,[1256] and others before them These studies have been reviewed by Ljungberg and the present discussion will be limited to the observations reported by this investigator.

Ljungberg has applied the Linderstrom-Lang technique to the microanalysis of sections 18 75μ thick cut from a 3 mm. core of rabbit kidney. He finds that the chloride concentration in such a column shows a characteristic concentration curve increasing from cortex to medulla (fig 63) In the outermost zone of the cortex the chloride concentration averages some 2 5γ per section (142 mg/100 gm.), the concentration increases slightly within the cortex, to drop abruptly to a minimal value at 3.50 mm from the surface, and to rise again progressively to figures in excess of 90γ per section (1000 mg/100 gm) at the apex of the medulla This figure exceeds the chloride concentration in any other known tissue The minimal value at 3 50 mm. depth coincides with the boundary between the cortex and the outer zone of the medulla, the region in which the thin limb begins to appear in significant numbers among the straight segments of the proximal and distal tubules and collecting ducts That the progressive concentration of chloride in the medulla is not attributable to urine in the collecting tubules is indicated by the facts, first, that the total area of these lumina and the thin segments is only some 8 per cent of the medullary cross section; and, second, the chloride content is apparently unrelated to the urine chloride concentration, which in Ljungberg's experiments ranged from 81 to 1089 and averaged 418 ± 64 mg/100 cc

When parallel sections are stained with a silver reagent, 'argentophilia' is practically absent from the thin segment, and only faintly present in the proximal tubule and thick descending limb, it is pronounced, however, in the distal convoluted tubules and more particu-

Nelson, Rosenbaum, and Strauss (pers. com.) have not confirmed Wolf with respect to the excretion of chloride during prolonged water diuresis. They find that, in normal subjects taking water at a rate of 20 cc/min. (300 cc. every 15 min.), diuresis begins within an hour and reaches a peak of 10 to 15 cc/min. within 2 hr., thereafter tending to decrease to as little as half the peak level despite the fact that water is accumulating in the body, as demonstrated by weight increase and dilution of plasma electrolytes, protein, hemoglobin, and hematocrit by as much as 10 per cent. In these experiments, prolonged water diuresis is accompanied by water retention rather than excess water excretion, but the intake exceeds the anticipated magnitude of facultative water excretion by a significant amount.

The urine chloride concentration and the rate of chloride excretion decreased to 5 mEq/liter and 0.03 mEq/min. at urine flows of 6 cc/min., and to 7 mEq/liter and 0.07 mEq/min. at flows of 10 cc/min., figures in sharp contrast to the figures of 34 mEq/liter and 0.28 mEq/min. reported by Wolf. Nelson *et al.* suggest that the maximal rate of diuresis depends on the salt load available for excretion; when salt has recently been ingested, or after preloading the day before, peak diuretic levels were attained almost twice as high as were ordinarily observed, and a diuresis of 10 cc/min. or higher was maintained for as long as 9 hr. Only by increasing the salt content of the body was it possible to avoid accumulating a positive water balance, and then this was accomplished only for the first few hours. This interpretation conforms with the view that the water available for facultative excretion is related to the distal load of sodium, as expressed above.

CYANIDED KIDNEY

Nicholson [1524] has perfused one dog kidney *in situ* with cyanided blood while using the other kidney as a control. The inulin and creatinine clearances remained unchanged and identical, but the reabsorption of water was greatly reduced, the U/P ratio of creatinine decreasing from the range of 50 to 191 down to 7.4 to 17.5. There was no evidence of back diffusion of creatinine, but the urea/inulin clearance ratio fell in the average from 0.58 to 0.33, showing excessive back diffusion of urea, and revealing that this ratio (at adequate urine flows) is a sensitive indicator of tubular integrity. The tubular excretion of phenol red was entirely abolished, this clearance falling to the level determined by unbound dye. The pH of the urine changed from acid (5.57 to 6.76) or alkaline values (7.92 to 7.98) to that of the blood (7.40 to 7.55). The urine volume increased from low levels (0.35 to 1.13) up to some 10 per cent

of the filtration rate (range 6.2 to 13 0), and the chloride U/P ratio fell from 2 or above down to exactly 1.0. Glucose excretion was only slightly increased. Although the author does not suggest this interpretation, the results are suggestive that cyanide may have a specific action on the distal tubule, blocking the distal reabsorption of sodium and water and the acidification of the urine by H^+ ion exchange; in the proximal tubule the only indicated action is the arrest of tubular excretion; the proximal reabsorption of glucose and of sodium appeared to be unimpaired.

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Ljungberg has applied the Linderstrom-Lang technique to the microanalysis of sections 18.75μ thick cut from a 3 mm core of rabbit kidney. He finds that the chloride concentration in such a column shows a characteristic concentration curve increasing from cortex to medulla (fig. 63) In the outermost zone of the cortex the chloride concentration averages some 2 5γ per section (142 mg/100 gm.), the concentration increases slightly within the cortex, to drop abruptly to a minimal value at 3.50 mm from the surface, and to rise again progressively to figures in excess of 90γ per section (1000 mg/100 gm.) at the apex of the medulla. This figure exceeds the chloride concentration in any other known tissue. The minimal value at 3 50 mm depth coincides with the boundary between the cortex and the outer zone of the medulla, the region in which the thin limb begins to appear in significant numbers among the straight segments of the proximal and distal tubules and collecting ducts. That the progressive concentration of chloride in the medulla is not attributable to urine in the collecting tubules is indicated by the facts, first, that the total area of these lumina and the thin segments is only some 8 per cent of the medullary cross section; and, second, the chloride content is apparently unrelated to the urine chloride concentration, which in Ljungberg's experiments ranged from 81 to 1089 and averaged 418 ± 64 mg/100 cc.

When parallel sections are stained with a silver reagent, 'argentophilia' is practically absent from the thin segment, and only faintly present in the proximal tubule and thick descending limb; it is pronounced, however, in the distal convoluted tubules and more particu-

larly in the collecting tubules.* The specificity of this method for the demonstration of intracellular chloride has been questioned by Lison,[1151] and the final interpretation of Ljungberg's studies must await further information on this point.

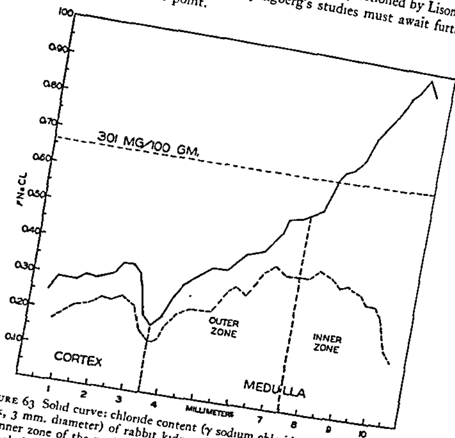


FIGURE 63 Solid curve: chloride content (γ sodium chloride per section 18.75 μ thick, 3 mm. diameter) of rabbit kidney from cortex to medullary papilla. In the inner zone of the medulla the concentration per unit volume exceeds that in whole blood (301 mg/100 cc.).

The dotted line shows the chloride distribution in the cyanide poisoned kidney. (Ljungberg [1150])

If it is accepted, as Ljungberg argues, that the intracellular argentophilic substance is chloride, it appears that the concentration of this ion in the collecting ducts reaches remarkable proportions. By various assumptions he calculates the intracellular chloride concentration to be

* The density of silver impregnation increases distally in the collecting tubules when chloride excretion is minimal, and recedes proximally when excretion is maximal. This observation presents difficulty in any interpretation.

less than 99 to 111 mg/100 gm. in the cells of the proximal tubules, and between 2500 and 2700 mg/100 gm., or 25 times more, in the cells of the collecting ducts. The plasma chloride in the rabbits with which he worked averaged 361 mg/100 cc., so that the calculations indicate an intracellular concentration in the collecting ducts some 7 times that of the plasma.

In rabbits killed 1 hr. after the injection of 2 cc. of 0 05 per cent potassium cyanide, the concentration of chloride, both as shown by histochemical analysis and silver staining, is reduced in the kidney as a whole and particularly in the distal system (fig. 63). Similar reduction is observed in Masugi nephritis[1257]

Ljungberg interprets his data as indicating that chloride reabsorption in the proximal tubule is a matter of passive diffusion, while reabsorption in the distal system is an active process and involves a step wherein chloride is concentrated within the cell However, the evidence for active reabsorption of sodium (with chloride as a passive anion) in the proximal tubule is so firmly established that it cannot be lightly set aside, and the *a priori* inference that active reabsorption requires cellular concentration is refuted (if we accept the specificity of Ljungberg's results) by the absence of a high intracellular chloride concentration in the proximal tubule Also negating this inference are the functional data on the failure of tubule cells to concentrate intracellularly substances which are actively excreted (phenol red, diodrast, and hippuran).

The intracellular concentration of chloride in the distal tubule and collecting ducts may be related to active chloride reabsorption as Ljungberg supposes; if so, it would seem that the mechanism concerns the reabsorption of sodium and not of chloride because, in the absence of an exchange anion (for which there is no evidence), chloride could not be reabsorbed without sodium, and indeed the evidence cited earlier in this chapter leads to the conclusion that it is sodium which is operated upon by the tubules and that chloride is an indifferent anion.

An alternative view, admittedly without evidential support but enticing as a speculation, is that an extraordinarily high intracellular concentration of (sodium? potassium? protein?) chloride is involved in the distal system in the reabsorption of water to form a hypertonic urine Under appropriate conditions water would diffuse into such an intracellular system by osmotic pressure to form a urine with an osmotic U/P ratio in excess of 1.0 In this theory, the water, once in the cell, would of course have to be disposed of, but this may be accomplished by metabolic disposal or by an osmotic pump that reconcentrates the intracellular electrolyte. Vaguely, the interpretation is more attractive

than the supposition that isotonic tubule cells abstract water molecules *per se* against the osmotic pressure of a hypertonic urine.

POTASSIUM

The potassium clearance under normal conditions is less than filtration rate [2259] and, since potassium is completely ultrafiltrable, it h been generally accepted that only tubular reabsorption is involved i its excretion. A potassium U/P ratio less than 1.0 has never been recorded, but this fact does not exclude active reabsorption.[2044] The regulation of the excretion of this cation is, however, very obscure. The clearance at normal plasma levels in man is independent of urine flow down to 0.6 cc/min, below which the clearance falls, possibly because of a reduction in filtration rate.[187, 855] It is said that in infants the clearance paradoxically varies inversely with the plasma level, but an abrupt increase in clearance, accompanied by a reduction in plasma level, is said to occur immediately after the oral administration of potassium salts [2232]

Isolated records of potassium clearances greater than inulin clearances [1109 1201] aroused no special interest until recently. Wirz [2313] records potassium/inulin clearance ratios in adrenalectomized cats of 1.41 and 1.55 at a time when the inulin clearance was very low, and he observed numerous ratios close to 1.0 when the inulin clearance was more nearly normal Subsequently Mudge, Foulks, and Gilman [1457] and Berliner and Kennedy [130] have independently shown that, under certain conditions in dogs, potassium-creatinine clearance ratios substantially above 1.0 may be obtained for protracted periods of time, an observation which has been confirmed by Wesson and Anslow (pers. com.) during osmotic diuresis. Mudge *et al.* found that the clearance ratio increased from 0 05 to 0.10 at normal rates of urine flow to 0.80 to 0.90 during marked urea diuresis, when the creatinine U/P ratio was about 2. At still lower creatinine U/P ratios the potassium/creatinine clearance ratio rose to 1.36. Similarly high ratios were obtained during the infusion of potassium chloride. The highest clearance ratio reported by Wesson and Anslow [2311] during mannitol diuresis was 0.95, but the ratio reached 1.91 during urea diuresis. Berliner and Kennedy found that with the preliminary oral administration of potassium chloride during the experiment, clearance ratios of 1.15 to 1.33 could be obtained for many successive periods.

It is assumed that extensive potassium reabsorption occurs in the proximal tubule, supplemented by tubular excretion in the distal system, and that the distal process, normally small, is increased during potassium overload in the body. This is the first instance in which it

has been necessary to postulate the simultaneous reabsorption and tubular excretion of any substance The physiological implications of such a double system are not clear.

The high potassium/creatinine clearance ratios are abolished by mercurial diuretics (Wesson and Anslow, pers. com.).[1498]

Berliner, Kennedy, and Hilton [182] find that, during the excretion of non-reabsorbable anions (ferrocyanide or thiosulphate), infusion of potassium regularly results in ratios of excreted to filtered which are higher than can be obtained during the excretion of chloride; the minimal tubular excretion of potassium so far exceeds the possible tubular excretion of anions that a cation exchange mechanism must be postulated.

Neutral potassium chloride and bromide when given intravenously lead to the excretion of a highly alkaline (pH 8.0 to 8 5) urine containing large amounts of bicarbonate [2219, 2258] The potassium clearance in normal cats appears to be generally independent of urine flow except under conditions of extreme oliguria where emptying errors may be large.[2249]

Conway, Fitzgerald, and MacDougald [399] have shown that the proximal tubule in the isolated frog kidney contains little intracellular sodium, although it can accumulate potassium against a gradient to upwards of three times its normal concentration They believe that the cells of the proximal tubule are 'impermeable' to sodium, but freely permeable to potassium and chloride. The distal tubule, which normally contains little potassium, does not accumulate potassium over the external concentration The authors argue against the interpretation that sodium and water are reabsorbed in the proximal tubule, because sodium does not accumulate in the cell. There is no reason to expect accumulation of sodium in the proximal tubule, however, if this ion is actively reabsorbed by this segment Substances undergoing tubular transport are not stored in the tubule cells. Phenol red, for example, is excreted by proximal tubules *in vitro* against a concentration gradient greater than 100 to 1, and yet no phenol red accumulates in the cell and the evidence is against the accumulation of diodrast or hippuran in the proximal tubule during excretion in man [1935] The absence of sodium from the proximal tubule implies active transport rather than otherwise.

CALCIUM, MAGNESIUM, AND STRONTIUM

Little is known concerning the specific features of calcium excretion except for the facts that the total excretion can be increased or decreased by varying the calcium and phosphorus intake, the acid-base forming properties of the diet, and by certain physiological means such as the

administration of parathyroid hormone. The deficiency in our knowledge on how calcium is handled by the kidneys arises in part from the complexity *of the physical-chemical state of this substance in the* plasma.

The total calcium content of normal human plasma ranges from 9 to 11.5 mg/100 cc. (2.3 to 3.0 mM/liter). Only about half of this is diffusible,[1279] the rest being combined with plasma proteins. Calcium and magnesium proteinates are probably much less completely ionized than are the corresponding sodium and potassium salts. The dissociation of calcium proteinate is affected by the protein and calcium ion concentration, and also by pH, temperature, albumin/globulin ratio, etc. In addition, the physiological activity of the diffusible calcium depends upon its electrochemical condition. It is well known that citric, tartaric, glycerophosphoric, and other hydroxy or dicarboxylic acids form poorly ionized calcium salts, while Greenwald [856] has adduced evidence that calcium and magnesium carbonates and phosphates are not completely dissociated, and that calcium, but not magnesium, forms a complex with carbonate and phosphate having the composition $Ca_2 \cdot PO_4 \cdot CO_3$. Calcium chloride may be thought of as nearly completely dissociated into calcium and chloride ions, the former being physiologically active, but the calcium in the organic complexes is not available in an ionic condition. Most investigators have favored the belief that a significant fraction of the plasma calcium is in the form of a non-ionized, non-protein salt of such a nature as calcium citrate,[694, 1134, 2063] a fraction which is sometimes designated as calcium-X. The physiological activity of calcium-X has been investigated by McLean and Hastings,[1347] using the excised frog heart, which is extremely sensitive to the ionic composition of the perfusion fluid, as a test for calcium ions. With this biological method they have concluded that the quantity of calcium-X is normally no greater than 0.5 mg. per cent; of the remaining calcium about half is present as calcium-proteinate and half as calcium ion.

It is to be expected that the excretion of calcium will not be related in any simple manner to the total calcium of the plasma. That portion combined with protein is unavailable for filtration, as perhaps is also much of the (colloidal?) phosphate complex, and it is probable that calcium-X and other complexes formed with carbonate and phosphate, as well as poorly ionized salts of organic acids with free phosphate groups, would not be handled by the kidney as are calcium ions. Hence, clearance studies must remain ambiguous until the state of calcium in the plasma is subject to better analysis.

Physiological control appears to be such as to maintain not so much a constant concentration of total calcium in the plasma as a constant concentration of physiologically active calcium[2068] One of the chief mechanisms involved in this regulation is the hormone of the parathyroid glands, which influences the equilibrium between plasma calcium and the calcium in the bones.

Calcium differs from sodium and potassium by the fact that when ingested much of it escapes through the bowel, only a small part appearing in the urine This is due to the circumstance that it is precipitated as insoluble salts in the alkaline intestinal fluids For this reason calcium chloride produces acidosis, in the net ionic balance it is as though hydrochloric acid were absorbed and calcium excreted as the carbonate, phosphate, or soap The belief that calcium and magnesium are excreted into the bowel is challenged by McCance and Widdowson[1302] on the grounds that during prolonged intravenous administration both salts are almost completely recovered in the urine without any increase in the fecal salt. However, the intestinal secretions probably contain not less than 1 mM/liter of calcium, and the total volume of these secretions is probably not less than 8 liters/day; if this salt is precipitated like orally administered calcium, it would be lost in the stool In this sense, it might be better to speak of the unavoidable loss of calcium, rather than its excretion, by way of the intestinal tract.

Nothing is known about the renal excretion of magnesium and strontium except that the kidney roughly distinguishes calcium from strontium, the latter being excreted more rapidly[1018] Only one-third to one-half of the intravenously administered strontium is rapidly excreted,[1303] but, of that which is excreted, 90 per cent appears in the urine That portion not excreted is deposited in the bones.

The administration of parathyroid hormone to normal dogs raises the total serum calcium and the filtrable calcium, and increases both the rate of tubular reabsorption and the rate of excretion The increased reabsorption can be attributed to the increased filtered load, and it is inferred that the hormone has no specific effect on tubular activity The hypercalcemia and hypercalcuria produced by the hormone are the results of its extrarenal actions in mobilizing calcium from body stores.[1067]

Dogs receiving steady intravenous infusions of calcium chloride or gluconate for 5 hr show no specific diuretic responses. The excretion of calcium under these conditions has been described by Wolf and Ball,[2260] but in the absence of data on plasma concentration these data are amenable only to empiric description.

IODIDE, ETC.

In experiments uncontrolled with respect to sodium excretion, the iodide clearance in the dog, at plasma levels of 5 mEq/liter, averaged about 17 per cent of the filtration rate.[800] But, on a low sodium chloride diet, the iodide clearance, at plasma iodide concentrations of 1.6 mEq/liter or less, ranged from 0.05 to 0.79 cc/min. Administration of sodium chloride increased the clearance to 17.7 cc/min., the iodide/chloride clearance ratio always being greater than 1.0.[1729] Inorganic radioactive iodide was cleared at a rate averaging 31 cc/min. of plasma in 7 normal subjects. Exclusive of observations 3 hr. or more after administration, the average clearance was 27 cc/min. in 11 patients with thyrotoxicosis. After 3 hr the plasma contains radioactive thyroxine, which invalidates renal clearance determinations.[1498]

The thiocyanate clearance in dogs is likewise very low (0 1 to 7.1 cc/min.) and related to the simultaneous excretion of (sodium) chloride, as shown by an increase in clearance after sodium chloride administration and by a positive correlation (P = +0.92) between thiocyanate excretion and chloride excretion.[2066] In man, Berger (pers com.) finds a chloride/thiocyanate clearance ratio ranging from 0.3 to 3 0, roughly scattered above and below 1 0. Breed (pers. com.) in 10 hypertensive subjects obtained thiocyanate-mannitol clearance ratios averaging 0.077 (0.038 to 0.20). The bromide clearance is likewise low, 22 observations in the dog (Berger, pers. com.) giving a bromide/chloride clearance ratio of 0.6.

Nitrate and chlorate are excreted very slowly, but no quantitative data are available

It may be recalled that iodide, nitrate, and thiocyanate are excreted by the aglomerular kidney (ch. 11).

CHAPTER XII

The Adrenal Cortex and Addison's Disease

In 1855, Thomas Addison identified the disease that bears his name with the complete destruction of the adrenal glands. Subsequent investigations have shown that the physiological disturbances in Addison's disease are apparently due to the deficient secretion of incompletely identified hormones elaborated by the adrenal cortex. A syndrome comparable in nearly all respects with Addison's disease can be produced in mammals by bilateral removal of the whole glands, or of the cortex alone. Complete bilateral destruction of the adrenal medulla is not lethal and is not related to adrenal insufficiency or Addison's disease. The most notable physiological defect in acute adrenal insufficiency is failure of sodium conservation by the kidneys, with consequent loss of sodium and water from the body, and progressive reduction of the extracellular fluid volume approaching lethal limits within a few days. Symptomatically, acute adrenal insufficiency is marked by the development of weakness, anorexia, prostration, vomiting, hypotension, dehydration, oliguria, and shock.

Most of the physiological disturbances in Addison's disease and in adrenalectomized animals appear to be secondary to oligemia (circulatory insufficiency, hypotension, tachycardia, feeble pulse and cyanosis, hepatic hypoxia and insufficiency, impaired glucose and fat absorption, elevated serum calcium, oliguria, azotemia)

since they can be partly or wholly alleviated by the administration of sodium chloride Some may, however, be related directly to impaired carbohydrate and protein metabolism, or to the unbalanced effects of other endocrine organs.

Bloody diarrhea is commonly present in the adrenalectomized dog, but even bloodless diarrhea is relatively infrequent in man. Chronic adrenal insufficiency in man is characterized by acute exacerbations which punctuate a progressively downward course. These 'adrenal crises' are most likely to occur following stress. Even in the absence of acute symptoms, the chronic Addisonian patient usually manifests asthenia, unusual susceptibility to fatigue, and a characteristic brown pigmentation of the skin and mucous membranes of the oral cavity, attributable to an increased production of melanin.[1974]

Baumann and Kurland[100] first called attention to a marked decrease in the plasma concentration of sodium and chloride and a rise in plasma potassium in adrenalectomized cats. Loeb[1258] showed that a significant decrease in plasma sodium concentration was characteristic of crisis in Addison's disease, and that the patient could be kept symptom-free by the addition of large amounts of salt to the diet. Loeb and his associates[1260,1261] and later Harrop and his coworkers[926] demonstrated that the decrease in plasma sodium in the adrenalectomized dog resulted from an abnormal loss of this cation through the kidney. It is now established[1966] that the sequence of events in acute adrenal insufficiency is referable in considerable measure to progressive reduction of body fluid as a result of failure of the renal tubules to reabsorb sodium, with secondary loss of water. This dehydration is reflected by an increase in hematocrit and some increase in serum protein concentration, and by a reduction of plasma and interstitial fluid volume. With increasing dehydration, renal function decreases and nitrogen, sulphate, and phosphate retention, fixation of urine specific gravity, and failure of ammonia formation follow. In untreated patients the plasma sodium may decrease 10 to 15 mEq below the low normal value of 140 mEq/liter, and during crisis to 100 mEq/liter. Plasma chloride usually decreases more than bicarbonate. During acute adrenal insufficiency, the plasma potassium may increase from the normal value of 4 to 5 mEq/liter to

double this value, and potassium intoxication is potentiated by excessive retention.

Even in the earlier stages of adrenal insufficiency, when sodium concentration and hence the osmotic pressure of the plasma is reduced, water shifts from the extracellular to the intracellular compartment, leading to increased water content in the tissues and aggravating the reduction in plasma and extracellular fluid volume [887, 1259, 2034, 2035, 2074]

The adrenal cortex is the source of many steroid compounds, some 28 or more having been isolated, while other active compounds of unknown composition remain in the amorphous residue. These compounds appear to have two general functions. The desoxycorticosterones, i.e those lacking a keto- or hydroxy-group at carbon 11, appear to be concerned primarily with the regulation of electrolyte balance, a function which (we presume on the present evidence and contrary to a number of earlier opinions) is mediated entirely by promoting the reabsorption of sodium in the renal tubules The pure compound which has been most extensively studied is the synthetic desoxycorticosterone acetate (DCA) It has not been demonstrated that desoxycorticosterone is a normal product of the adrenal cortex, the only substance isolated from the adrenals that has strong sodium-retaining power is chemically wholly unlike desoxycorticosterone and has no effect on potassium excretion * [2060] Some of the cortical steroids exist in chemical union with ascorbic acid. The increased reabsorption of potassium characteristic of adrenal insufficiency may be related to failure of sodium reabsorption, or it more probably reflects an independent renal disturbance.[921, 1719, 2299] It is significant, however, that potassium retention does not occur if the sodium intake is adequate to maintain sodium balance.

That the renal conservation of sodium is, so far as short periods of time are concerned, the most important action of the adrenal cortex is demonstrated by the fact that adrenalectomized animals can be maintained in a moderately good state of health for indefinite periods simply by increasing the dietary intake of salt.

* The synthetic compounds, corticosterone and dehydrocorticosterone, though less effective than desoxycorticosterone, have a similar action on the renal conservation of sodium and the excretion of potassium

Conversely, the clinical picture of acute adrenal insufficiency can be induced in the Addisonian patient by restricting the intake of salt to about 1.5 gm/day, and corrected, except in its terminal stages, by increasing the salt intake.

The second established function of the adrenal cortex concerns the intermediate metabolism of protein and carbohydrate, especially under conditions of emergency demand. The synthetic compound E of Kendall (11-dehydro-17 hydroxycorticosterone, cortisone) is highly potent in this respect.[1203] It is not know whether or not this compound is normally elaborated by th adrenal cortex. That it is not essential for life is shown by the fac that Addison's disease can, except for emergencies, be treated as successfully either with DCA or dietary salt as with whole cortical extract. Compound E induces moderate retention of salt and water.[1692] It has attracted attention because of the dramatic relief of rheumatoid arthritis and other conditions effected by its administration in relatively large and probably unphysiological doses.

The adrenal cortex also elaborates androgenic and estrogenic substances, but so far as is known these have no relation to renal function.

Selye[1881] has reported extensive studies of the role of the adrenal cortex in what he calls the 'alarm reaction.' Adrenalectomized animals are especially susceptible to many forms of stress such as cold, anoxia, hemorrhage, burns, acute infection, etc. Such trauma regularly cause enlargement of the adrenal glands in normal white rats in the course of a few hours, while some of them at least have been shown to bring about rapid depletion of the ascorbic acid content of the glands, perhaps indicating rapid excretion of a 'mother compound.' In such traumatized animals there is also a decrease in the cholesterol content of the glands and an increased excretion in the urine of material which prolongs the life of adrenalectomized rats, and which increases the storage of glycogen in the liver of fasted, adrenalectomized rats. This urinary corticoid material is presumed to be of adrenal origin. During these 'emergencies,' the requirement for adrenal steroids of the compound E type is increased, and adrenalectomized animals or patients with severe Addison's disease main-

tained only with DCA or salt continue to be susceptible to severe spontaneous hypoglycemia and other metabolic disturbances which may prove fatal under conditions of stress.

ADRENOCORTICOTROPHIC HORMONE (ACTH)

The adrenal cortex is under the trophic influence of the adreno-corticotrophic hormone (ACTH) of the anterior pituitary gland, and hypophysectomy leads to atrophy of the cortex unless ACTH is administered Dougherty and White [440] have shown that both ACTH and adrenal cortical extract cause disintegration of lymphoid tissue, a process which is accompanied by an increase in circulating gamma globulin believed to be liberated from this tissue. This increase in gamma globulin results in an increase in circulating antibodies. There is simultaneously an increased excretion of uric acid, presumably resulting from accelerated nucleoprotein metabolism Thorn, Prunty, and Forsham [1075] have devised a test for adrenal competence based upon the administration of a single dose of ACTH to stimulate cortical secretion; the test is considered positive if the uric acid/endogenous creatinine ratio is increased in a urine sample collected during a period of 1 to 3 hr. after injection of 25 mg of ACTH, and if the eosinophil count shows a sharp drop 11-Hydroxycorticosterone gives a positive Thorn test, but DCA is without effect. Adrenalin has a similar action on the eosinophil count and the lymphoid tissue, since it stimulates the secretion of ACTH. It is not yet established that the increased excretion of uric acid is a result of increased production rather than decreased tubular reabsorption.*

GENERAL EFFECTS OF DCA IN NORMAL ANIMALS

Because of the ready availability of the pure synthetic preparation, DCA has been more extensively studied than any other compound related to the cortical steroids. As noted above, it is not yet determined that desoxycorticosterone is a normal product of the adrenal gland. Administered in excessive amounts to normal animals and men, DCA induces sodium † and water retention, increased potassium excretion,

* It will be recalled that a wide variety of compounds interferes with the tubular reabsorption of uric acid

† Contrary to its usual action in normal subjects, DCA increases sodium excretion in patients with Cushing's syndrome [illegible]

and a decrease in plasma potassium.[2072, 2073] Plasma sodium may be elevated some 5 or more mEq/liter. Prolonged administration of DCA to normal dogs leads to muscle weakness with replacement of as much as 30 per cent of the muscle potassium by sodium. The blood pressure is increased in patients in whom hypertension had been present before the onset of acute adrenal insufficiency, and the development of hypertension has been reported [1691] in patients treated with DCA in whom there was no evidence of previous hypertensive disease, while hypertension and cardiovascular and renal lesions have been produced in normal rats treated with massive doses of DCA and salt.[1845] This hypertensive effect has not been confirmed, however, in dogs on a high salt diet.[2024] Woodbury, Cheng, Sayers, and Goodman [2270b] find that the effects of large doses of DCA in elevating the plasma concentration of sodium and decreasing that of potassium is antagonized by ACTH, and they believe that large doses of DCA produce a deficiency of adrenal cortical secretion by inhibiting the adrenocorticotrophic activity of the anterior pituitary. They suggest that hypertension, increased size of the heart and kidney, nephrosclerosis, and other cardiovascular changes produced by DCA in experimental animals are toxic manifestations resulting from excess exogenous DCA and a deficiency of 11,17-oxysteroids consequent to inhibition of pituitary activity.

Massive doses of DCA in normal dogs and rats lead to the development in a few weeks of polydipsia and polyuria, which are exaggerated by the dietary administration of excess salt (potassium chloride is without specific effect). Polyuria cannot be produced in DCA-treated rats on a low salt diet.[754, 1176, 1494, 1668] In neither species does the rate of fluid excretion approach the magnitude reached in diabetes insipidus, however, and, unlike diabetes insipidus, pitressin has only a moderate antidiuretic effect. This polyuric action is exaggerated by hypophysectomy.[438, 636, 1668, 1533, 2242] Water and saline diuresis are accelerated by DCA and cortical extract, but the return of water is not increased.[754, 1494] DCA in doses up to 30 mg/day does not increase the water exchange of normal cats, and in this species it does not exaggerate diabetes insipidus.[2242] Normal man, given smaller doses than necessary to produce polyuria in dogs, responds to DCA by retaining sodium and water.[2071, 2292]

The increased urine flow induced by large doses of DCA (other adrenal corticoids are apparently not active in this respect) is frequently likened to diabetes insipidus, but the parallel is unsafe. Gaunt, Birnie, and Eversole,[754] in reviewing this and related problems, note that two factors are involved: (a) augmentation of thirst as a result of sodium re-

tention; and (b) an assumed inhibition of tubular reabsorption of water. The evidence for the latter is, however, based largely upon the damping of water diuresis in adrenal insufficiency, the presumption being that this is due to the absence of some 'diuretic' potency in the adrenal gland. The problem is too complex for so simple an interpretation The questions of electrolyte distribution between tissues and extracellular fluid, the concentration of sodium in the plasma, changes in the filtration rate and sodium load delivered to the distal tubule, and a possible toxic effect of large doses of DCA on the tubules themselves, all require further investigation before a physiologically specific 'diuretic' activity can be attributed to DCA or any of the naturally occurring adrenal hormones.

Rusznyak, Foldi and Szabo [1763] report that desoxycorticosterone glucoside (percorten), administered intravenously, greatly increases Tm_G They suggest that this effect results from an increase in phosphorylation in the renal tubules The phenomenon was absent in alloxan-treated animals [667] However, Lambert, Lebrun, and de Heinzelin de Braucourt [1196] report that in 10 patients the administration of percorten intravenously decreased Tm_G by an average of 30 per cent The filtration rate, as measured by thiosulphate, was not altered Five control experiments showed that the repeated intravenous injection of glucose did not change Tm_G, and the solvent (acetamide-glucose) was without effect The authors are examining the question whether this action of percorten is to be attributed to the fact that it is a glucoside.

Friedman, Polley, and Friedman [721] report that DCA pellets, subcutaneously implanted in rats, produce hypertension, cardiac hypertrophy, and altered renal function, the concomitant feeding of 1 per cent saline intensifies the renal changes The plasma concentrations of potassium and chloride are initially decreased, the sodium concentration and the sodium/chloride ratio are increased, the sodium concentration and potassium concentration are increased, and finally both sodium and potassium concentration are increased. Calcium excretion is unaffected Their interpretation of alterations in renal function following DCA administration are not completely validated by their data. They state that the alteration in renal function consists first of a reduction in the PAH clearance, but that the blood flow to each unit of functioning excretory tissue is normal so that no ischemia is present * Later the quantity of functioning tubular tissue decreases, while the renal plasma flow decreases even more, so that relative renal ischemia occurs

* The C_{PAH}/Tm_{PAH} ratios appear to be incorrectly calculated in some instances, but estimations from the means of the two terms would not alter this conclusion

In this stage, gross interference with filtration is assumed to be present. However, examination of their data reveals that DCA alone had no apparent effect on renal function. The animals treated with DCA and saline did not differ from the untreated or saline controls at the end of the second week; at the end of the fourth week C_{PAH} had decreased, but only at the end of the sixth week was there a probably significant decrease in C_{PAH} and Tm_{PAH}. Apart from the interpretation of the data as presented, the normal data on C_{PAH} and Tm_{PAH} presented elsewhere (ch. XVII) by Friedman and his coworkers differ significantly from the data reported by other investigators for this species. It should be noted that the technique of renal clearance determination in rats is not satisfactory to all investigators, and observations in this species must at the present time be accepted with reservations.

Swingle and Remington [2035] concluded that DCA and related hormones directly influence the distribution of electrolytes and water between the extracellular fluid and the tissues. Gaudino and Levitt [760] have re-examined the question, using isotopic, Na^{24} and K^{42}, inulin as a measure of extracellular space, and D_2O as a measure of total body water. They find that the administration of DCA to two normal dogs led to expansion of the extracellular space (+40 to +53 per cent) at the expense of the intracellular space (−33 to −43 per cent), the intracellular concentrations of sodium and potassium being reciprocally elevated at the peak of the response. The filtration rate increased (+37 to +53 per cent), as did the renal plasma flow (+23 to +42 per cent), while Tm_{PAH} decreased (−26 to −74 per cent). Serum potassium fell to nearly half its control value, plasma sodium remaining unchanged. Total body sodium increased by 30 per cent over a period of 16 days, with a simultaneous increase in the average intracellular concentration of this ion.

Administration of cortical extract led, conversely, to expansion of the intracellular space (+25 to +39 per cent) and total body water (+30 to +49 per cent), with no alteration in the extracellular space and with no consistent changes in filtration rate or renal plasma flow. Tm_{PAH} showed marked but contradictory changes. Plasma sodium, potassium, and NPN did not change significantly. The effects of DCA and cortical extract in normal animals were transient, all variations tending to return toward normal on continued treatment, as others have observed.* That DCA in large enough doses increases the filtration rate and renal plasma flow in normal dogs has also been reported by Collings, Down-

* The effects of DCA in the adrenalectomized dog were, however, persistent, suggesting that the adrenal gland may itself destroy DCA.

ing, and Hodges,[297] who attribute these effects to increased circulating blood volume (increased extracellular fluid?).

RENAL FUNCTION IN EXPERIMENTAL ADRENAL INSUFFICIENCY

Harrison and Darrow[921] first showed that bilateral adrenalectomy in dogs is followed by reduction in filtration rate and urea clearance to some 25 per cent of the control values, an effect only partly corrected in their experiments by salt or cortical extract. They attributed the high concentration and consequent excessive excretion of sodium in the urine of the adrenalectomized dog to failure of tubular reabsorption. On the other hand, the 'maximal' U/P ratio of potassium was reduced from 40 to 75 in the normal to 10 after adrenalectomy, and they believed that this circumstance, combined with oliguria, led to potassium retention. The administration of salt, in their view, by replacing the sodium deficit in the body fluids, increases the filtration rate and urine flow and thus permits the excretion of greater quantities of potassium at a low U/P ratio, reducing the plasma potassium concentration. Cortical extract, on the other hand, not only increases urine volume but also the maximal potassium U/P ratio (from 10 up to 20 to 35) Roemmelt, Sartorius, and Pitts[1139] also conclude that the retention of potassium is a manifestation of increased specific reabsorption of this cation and not directly related to diminished sodium excretion.

The evidence seems convincing that, in the untreated animal, adrenalectomy rapidly leads to reduction of the filtration rate and modification of other renal functions Friedman *et al*[719] report that 1 day after adrenalectomy in the rat the PAH clearance and Tm_{PAH} are reduced but the inulin clearance is unaffected Renal function returns to normal in 6 days. The data were, however, obtained by comparing sham-operated animals with adrenalectomized animals Boss, Birnie, and Gaunt[216] report a 33 per cent decrease in filtration rate in rats 5 days after adrenalectomy

Wirz[2249] reports marked reduction in the filtration rate in adrenalectomized cats, and Gaudino and Levitt[730] find a marked and rapid reduction in filtration rate, renal plasma flow, and Tm_{PAH} in adrenalectomized dogs These, and all clinical studies in man, support the inference that the adrenal-deficient organism is delicately poised with but a small margin of safety in salt and water balance and, without perfect maintenance of the latter, slips quickly in exsiccation with significant reduction in renal function merely because of this exsiccation The im-

portance of more adequate knowledge on the filtration rate in this problem cannot be overemphasized.

If maintenance therapy with either sodium chloride, DCA, or cortical extract is adequate, the filtration rate is apparently not reduced by adrenalectomy *per se*.[719, 2205, 2249] Lotspeich[1274] found that the creatinine clearance in adrenalectomized rats maintained on a high salt diet averages 0.490 cc/100 sq. cm, as compared with 0.513 cc/100 sq. cm in controls fed *ad libitum* and 0.467 cc/100 sq. cm. in salt-fed controls; while Roemmelt, Sartorius, and Pitts[1739] found no reduction in filtration rate in adrenalectomized dogs maintained with cortical extract It seems probable that Harrison and Darrow's dogs did not receive adequate maintenance therapy.

The filtration rate, renal plasma flow, and Tm_{PAH} are not changed when calculated on a surface-area basis in normal or adrenalectomized rats treated with DCA and saline, but are decreased on the basis of kidney weight because of renal hypertrophy.[717]

The administration of adrenal cortical extract had no marked effect on Tm_D in normal or 'puncture' dogs (the slight changes were negative), or in hypophysectomized dogs, in which this function is reduced to low levels. It also had no effect on the diodrast clearance in normal, puncture dogs or hypophysectomized dogs, and only slight positive effects on the inulin clearance.[946]

Very mild adrenal insufficiency, asymptomatic and with normal blood volume and NPN, sodium, and potassium levels, was, however, accompanied by decreases in the diodrast clearance and Tm_D as marked as those observed after hypophysectomy, with small decreases in the inulin clearance. DCA pellets restored renal function toward normal The asymptomatic, adrenal-deficient dog did not respond, as did the normal or the hypophysectomized dog, to anterior lobe extract with increases in clearances and Tm_D, despite the fact that the action of the hypophysial hormone is directly on the kidney and not mediated through the adrenotrophic hormone[2204, 2206]

In Gaudino and Levitt's study,[750] during adrenal insufficiency the intracellular space increased (+15 to +30 per cent) while the extracellular space decreased (−59 to −61 per cent) * Plasma volume is said to have remained fairly constant at mild degrees of insufficiency, when changes in the other compartments were prominent (the specific gravity of the plasma and the hematocrit were increased, however). The usual

* Similar qualitative changes are reported in adrenalectomized dogs by Flanagan and Overman,[661] using the less reliable methods of thiocyanate for total body water and the single injection of mannitol for extracellular fluid.

signs of adrenal insufficiency were present: plasma sodium decreased and plasma potassium and NPN increased. The filtration rate, diodrast clearance, and Tm_{PAH} all decreased.

Gaudino and Levitt conclude that the adrenal cortex has a primary influence on the equilibrium distribution of fluid between the extracellular and intracellular compartments. DCA produces a decrease in the intracellular and an increase in the extracellular space; adrenalectomy has the reverse effect. Cortical extract simulates adrenalectomy in increasing the intracellular space, but it does not significantly modify the extracellular space. If DCA reflects the action of an adrenal hormone, the dissimilar actions of DCA and cortical extract may reflect a possible opposing role on the part of the physiological hormones.*

The shifts of water between the intracellular and extracellular compartments cannot be related solely to the concentration of electrolytes in these compartments. In normal dogs during DCA treatment, water moved out of the cells at a time when the plasma sodium was unchanged, and against an increased intracellular cation concentration; while treatment with cortical extract led to expansion of the intracellular space with no change in plasma sodium concentration. At the height of adrenal insufficiency, water again shifted into the cells despite an unchanged plasma sodium concentration. Assuming that osmotic equilibrium between plasma and tissues obtains at all times (an assumption that has not yet been proved), these facts indicate that adrenal activity influences the osmotically active constituents within the cell, other than sodium and potassium, so as to alter the effective intracellular osmotic pressure.

These investigators note that in the normal animal some mechanism operates to maintain the volume of the extracellular space remarkably constant. After adrenalectomy, it may be conceived that continued loss of sodium and water make it impossible for this mechanism to operate, that there is no specific impairment of the regulatory mechanism is indicated by the fact that the extracellular space is approximately preserved by the administration of salt alone, and changes in extracellular fluid volume are still reflected in changes in filtration rate and renal plasma flow, as in the normal animal. Apparently the adrenal gland is not necessary for the regulation of the filtration rate in relation to extracellular fluid volume. But, in DCA-treated animals, both normal and adrenalectomized, the extracellular space is excessively expanded, indicating that DCA somehow disturbs the mechanism regulating the vol-

* The adrenal cortical extract used did not contain significant quantities of DCA.

ume of this compartment without specifically blocking the control of glomerular activity.

On DCA injection, plasma volume did not increase in 2 out of 3 dogs, despite 60 and 52 per cent increase in extracellular space, and in severe insufficiency the decrease in extracellular fluid on a percentile basis was about twice the decrease in plasma volume This dissociation indicates that plasma volume is not a sensitive index of extracellular space.

Under conditions of dehydration, the maximal concentration of urine of the adrenalectomized dog, as judged by specific gravity and chloride content, is considerably less than normal.[1152] So, too, in persons with Addison's disease the maximal concentration of sodium in night (oliguric) urine samples is less than in normal subjects, while the concentration tends to remain fixed after the ingestion of water because of damped water diuresis. These two circumstances lead to fixation of urinary concentration at an intermediate value, a phenomenon which has been made the basis of diagnostic tests for Addison's disease.[1697,1734]

In adrenalectomized animals and Addisonian patients, water diuresis is typically diminished in extent and water excretion delayed in time.[753,754,757,1182,1734,1878] This blunting of diuresis is said to be uncorrected by the administration of salt, despite the fact that, in adrenalectomized dogs maintained on a high sodium, low potassium diet, the urine formed at the peak of water diuresis is as dilute or nearly as dilute as that obtained in intact animals. Abrupt water diuresis is in part restored by cortical extract, compound E, and the 11-oxygenated cortical steroids, but DCA is less effective.[218,754,1274,1739] It seems probable that the blunting of water diuresis is attributable in great part to reduced filtration rate, which results in reduced load of sodium and therefore water delivered to the distal system, supplemented perhaps by continuous secretion of ADH.

Diminished water diuresis in adrenal insufficiency is not related to the absence of the adrenal medulla Bilateral demedullation in rats has no effect on the course of diuresis, even though the injection of adrenalin into normal animals under certain circumstances augments the diuresis to such an extent that dehydration may result even while water is being administered.[756]

Adrenalectomized animals develop water intoxication after the retention of less water than is required in normal animals, a sensitivity corrected to some extent by adrenalin, which increases the diuretic response in the rat;[752,944,2036] by DCA; and, more effectively, by compound E.[611] The protective action of DCA is in part attributable to the promotion of diuresis,[176] (possibly because of an increase in the filtra-

tion rate) and possibly in part because of changes in the electrolyte content of the tissues and extracellular fluid

Unilateral adrenalectomy moderately increases renal function on the operated side, but apparently only by interfering with the renal innervation.[1171]

Plasma urea and NPN are reported to rise in adrenalectomized dogs maintained on DCA, while plasma sodium and potassium and the filtration rate are still normal. There is no decrease in the urea/inulin clearance ratio, and hence elevation of plasma urea implies increased protein metabolism [2205]

ACTION OF DCA ON SODIUM REABSORPTION BY THE RENAL TUBULES

It has been widely assumed that DCA acts directly on the renal tubule to promote sodium reabsorption, and that it is simply the absence of this positive effect that leads to increased sodium excretion in adrenal insufficiency. Some investigators, however, have suggested a more complicated interpretation.

Silvette and Britton [1893] reported that adrenalectomized opossums do not excrete sodium as readily as do controls and, consequently, they show a greater rise in serum sodium and chloride concentration after saline administration. Cortical extract increased sodium excretion in both normal and adrenalectomized animals receiving distilled water, though the effects were variable when saline was given Posterior pituitary extract increased sodium excretion in adrenalectomized animals, an effect evident to a lesser if not negligible degree in normal animals. Oliguria is characteristic of adrenalectomized opossums as of other mammals, and during oliguria there is a general tendency for the urine flow to vary with sodium excretion; since the urine flow was increased by cortical extract in both normal and adrenalectomized animals (perhaps more so in the latter), Silvette and Britton spoke of this extract as being 'diuretic,' and concluded that there is a specific hormone of the adrenal cortex that acts in the kidney to produce (water) diuresis, antagonizing the influence of ADH. Their interpretation clearly defines the antagonism in terms of the reabsorption of water by the renal tubules, a view which then and now is unwarranted, since the filtration rate may have been increased in both normal and adrenalectomized animals (more so in the latter), thus delivering more sodium and water to the distal system and promoting either sodium or water diuresis. Because ADH inhibits water diuresis, Silvette and Britton spoke of a

physiological antagonism between the adrenal gland and the neurohypophysis. Such antagonism has also been inferred from the circumstance that adrenalectomy prevents transient polyuria in hypophysectomized rats.* [434] The demonstration that DCA reduced sodium excretion, whereas pitressin increased it,[433] shifted the supposed antagonism between the adrenal cortex and the neurohypophysis to the reabsorption of sodium, rather than water, a view which has recently received support from Pitts and his coworkers.

Roemmelt, Sartorius, and Pitts [1739] have shown that the adrenalectomized dog, when given saline, concentrates sodium to as great a degree or greater than does the normal animal, showing that a reduction in the limiting maximal concentration of the urine *per se* cannot explain the renal deficiency in reabsorption. They find, however, that in the adrenalectomized dog the capacity to excrete sodium after saline administration is reduced, as is the capacity to excrete water. The depression of water diuresis they attribute to overproduction of ADH and/or increase in sensitivity of the renal tubules to this hormone, since Birnie *et al.*[178, 754] have reported an increased quantity of antidiuretic and chloruretic substance in the blood of adrenalectomized rats.† In their view, increased secretion of ADH (or increased sensitivity of the tubules to ADH) leads to excessive water reabsorption, and the resulting oliguria leads, by a mechanism that is not clear, to an increased reabsorption of sodium; this is in turn reflected in an inability to excrete this ion with normal effectiveness after loading the body with saline. They attribute the loss of sodium from the body at normal loads, the cardinal feature of adrenal insufficiency, to the natriuretic effect of ADH, present in maximal concentration in this condition; the hypothesis in this form thus shifts the explanation of the failure of the kidney to conserve sodium from a deficiency of DCA and its positive action on sodium reabsorption to the excessive natriuretic effect of ADH. This theory of a reciprocal or antagonistic action between ADH and DCA is extensively developed by Gaunt, Birnie, and Eversole [754] in the interpretation of the symptom complex of adrenal insufficiency.

* The blunting of polyuria in hypophysectomized animals has an adequate explanation in the marked drop in filtration rate (ch. xv) without further complicating a surgically and physiologically involved situation by adrenalectomy

† The questionable significance of such tests is discussed in chapter x

Certain observations of Winter and his colleagues are of interest in this connection. The injection of 3 units of pitressin 3 times daily leads to a strongly negative sodium and chloride balance in cats, but the effect is temporary and is followed by a compensatory retention whether the injections are continued or not. Salt excretion is said to be much less affected in diabetes insipidus animals than in normals, a circumstance which appears to apply to man (ch x).

The transient polyuria and the onset of permanent polyuria in diabetes insipidus cats are both accompanied by abrupt, parallel increases in chloride excretion, but compensation occurs within 2 or 3 days so that ultimately chloride balance is re-established despite the absence of ADH

After adrenalectomy, cats with diabetes insipidus show an early negative sodium balance similar to adrenalectomized animals with intact neurohypophysis. Since the neurohypophysectomized-adrenalectomized animals die sooner than do animals with intact hypophysis, their postadrenalectomy loss of electrolyte is, in the total, not so great. Such animals do not show the decreased plasma sodium and chloride concentration characteristic of adrenalectomy, presumably because of concurrent loss of water, but the characteristic increase in potassium still occurs.

The facts that adrenalectomy leads to a negative sodium balance in the diabetes insipidus animal, as in the animal with intact neurohypophysis, and that pitressin has little or no natriuretic activity in patients or animals with diabetes insipidus require reconciliation with the theory of Roemmelt *et al.*, i.e. that natriuresis is attributable to excess secretion of or increased sensitivity to ADH.*

Sartorius and Roberts [1770] re-examined the problem in the dog and found that, in well-hydrated dogs (40 cc/kg. *per os*), pitressin in single doses of 0.8 to 8.0 milliunits/kg. produced, after a latent period of about 15 min., an increase in sodium excretion which at the larger dose amounted to a maximum of 100 microEq/min. and

* The fact that when pitressin is given to adrenalectomized cats the excretion of sodium is not increased as in the normal animal [illegible] is compatible with the theory of pre-existing maximal ADH activity, if such maximal activity can be firmly established

lasted for 80 min. or more. Antidiuresis was present for the first 30 min. and was succeeded 1 to 1½ hr. later by an increase in urine flow of undetermined origin, which on occasion reached 4 to 5 cc/min. The intravenous administration of DCA (80 microgm/kg.) in a sesame oil-aqueous emulsion to hydrated dogs excreting sodium at rates within 10 and 30 microEq/min. led, after a latent period of 45 min., to a sharp decrease in sodium excretion which lasted for some 75 min. This decrease in sodium excretion was accompanied at first by a moderate reduction in urine flow, but ultimately resulted in diuresis. DCA had no effect on urine flow in dogs hydrated in the standard manner, or upon the retardation of diuresis effected by 0.8 milliunits of pitressin given 15 min. after the water load. The authors therefore conclude that DCA has no effect on water diuresis *per se*, or on the action of pitressin on water diuresis.

But when pitressin (0.8 milliunit/kg.) was combined with DCA in increasing doses, the natriuresis characteristic of pitressin was progressively reduced, reaching a low value of 18 per cent of the control rate established by pitressin alone when the dose of DCA was 80 microgm. The authors suggest a quantitative relation between the two agents, as suggested by Silvette and Britton. Both DCA and pitressin independently increased potassium excretion, and, when given in combination, showed almost complete summation in this respect. The authors believe that all these effects are independent of changes in the filtration rate.

Sartorius and Roberts thus find no evidence that DCA exerts a diuretic action (referable specifically to water reabsorption or antagonism to ADH). They do, however, affirm the conclusion that sodium excretion, at least within certain limits, is determined by the balance between the natriuretic effect of ADH and the sodium conservation effected by DCA (or a similar hormone in the body). In adrenal insufficiency, excessive pitressin secretion leads to sodium loss by inhibition of sodium reabsorption.*

* They note that the 'diuretic activity' of DCA was established on long urine collection periods, which are complicated by variable water intake, and that others [1494, 1668] have presented evidence that the polyuria of DCA intoxication is secondary to polydipsia; DCA leads to increased sodium reabsorption and secondarily to an increased filtration rate [illegible] and/or increased water intake.

Sartorius and Roberts attribute the retention of potassium in adrenal insufficiency to the absence of a DCA-like hormone which inhibits potassium reabsorption, supplementing the similar action of ADH. The blunting of water diuresis they attribute to the unopposed action of excessive ADH secretion or to increased sensitivity of the renal tubules to this hormone.

The foregoing theory requires that pitressin possess a sustained natriuretic effect in all pertinent circumstances * in adrenal-deficient animals, and that an increased secretion of ADH be characteristic and invariable in all conditions involving failure of sodium conservation in the adrenal-deficient animal, or that the tubules be hypersensitive to this hormone.† If the premises are acceptable, the theory may be said considerably to reduce existing chaos.

Clearly, however, a final interpretation of the action of DCA and other adrenal cortical hormones on the tubular reabsorption of sodium and water must await further investigation. It may be tentatively accepted (as has so long been believed) that DCA (and a DCA-like hormone from the adrenal cortex) specifically increases sodium reabsorption in the renal (distal?) tubule; and that, in appropriate doses and under certain circumstances, ADH inhibits sodium reabsorption in the renal (distal?) tubule. But, if the data on water diuresis are correctly interpreted (ch. x), the secretion of ADH is a highly labile function, ranging from very little in habitual water consumers to almost continuous activity in men living under arid, dehydrating conditions. On the other hand, the sodium balance of the body (to repeat) is one of the most carefully guarded features of the *milieu interieur*. Consequently, to suppose that sodium balance is inversely (and precariously) related to water balance goes against the basic physiologic facts that men do not go into exsiccatory (equivalent to adrenal) failure during prolonged dehydration so long as extrarenal salt loss is

* Several reports have been cited in chapter x indicating that pitressin has no natriuretic action in normal subjects or dogs during water diuresis or in diabetes insipidus

† The difficulty of interpreting all tests for ADH, even by the use of massive quantities of concentrated urine (much less small quantities of plasma), has been noted in chapter x The postulate of hypersensitivity to ADH is, at the moment, perhaps gratuitous.

avoided, or develop edema as a result of protracted hydration. It is perhaps worthy of note that two factors may have opposite effects, without being physiologically antagonistic in the regulation of a steady state: *viz.* insulin and adrenalin, or synaptic fatigue and skeletal muscle tone.

The retention of potassium Pitts and his coworkers attribute to a specific increase in the reabsorption of this ion, unrelated to sodium reabsorption, since the time courses of the action of DCA on the two processes are different. That the retention of potassium is a renal affair is shown by the fact that neither DCA nor cortical extract influences the rising plasma level of potassium in nephrectomized dogs, i.e. these hormones are without effect upon the distribution of potassium within the body.[2240] Wirz [2249] reports that the potassium clearance is consistently reduced in adrenalectomized cats during insufficiency, but may nevertheless exceed the inulin clearance by 40 per cent or more.

The administration of cortical extract and of DCA to adrenalectomized dogs in the experiments of Roemmelt *et al.* led to an increase in renal plasma flow substantially greater than was observed during salt maintenance, with no change in filtration rate and despite the fact that the filtration rate had not been reduced before adrenal therapy.

RENAL FUNCTION IN ADDISON'S DISEASE

Margitay-Becht and Gomöri [1384] were the first to attempt to assess the filtration rate in patients with Addison's disease. In 3 patients they found values for the creatinine clearance of 68, 63, and 56 cc during crisis, figures far below normal. Therapy with cortical extract increased these figures to 105, 109, and 144 cc., practically within the normal range. McCance [1290] reported a single patient not in crisis who had an inulin clearance of 50 cc.

Talbott, Pecora, Melville, and Consolazio [2043] studied 10 patients with chronic adrenal insufficiency, some of whom suffered pan-hypopituitarism. In most instances the patients were well compensated at the time of study and the renal changes, therefore, reflected the chronic effects of adrenal insufficiency rather than the disturbances of crisis. All Addisonian patients showed a low normal to very low filtration rate. DCA therapy increased the

filtration rate by an average of 32 per cent, cortical extract producing no greater improvement. Limited observations on the diodrast clearance showed proportionately less reduction in renal plasma flow, and a somewhat low filtration fraction. The filtration rate was also markedly reduced in the patients with pan-hypopituitarism, and the diodrast clearance was very low in the 2 patients studied. In the few patients examined in both groups glucose Tm was markedly decreased, diodrast Tm only slightly so.

Sanderson [1766] reported that the inulin clearance in 4 Addisonian patients during periods of insufficiency ranged from 55 to 58 per cent of normal, the diodrast clearance from 58 to 77 per cent of normal, but a Tm_D had a value ranging from 61 to 92 per cent of normal, but a specific deficiency in this value cannot confidently be inferred from the data, especially in view of the reduced renal blood flow. The filtration fraction was low or low normal. Treatment with salt and DCA increased the filtration rate in only 2 subjects and the plasma flow in 1 but the filtration fraction increased in all 4. Treatment had slight positive effect on Tm_D. He suggested that the consistent rise in filtration fraction is related to the rise in blood pressure under therapy.

Waterhouse and Keutmann [2150] studied 13 Addisonian patients who were receiving either salt therapy or DCA and who were in good clinical condition at the time of examination. In 7 women the filtration rate, renal plasma flow, and Tm_{PAH} were consistently below the normal limits.* Renal blood flow and filtration rate were also subnormal in all 6 men; renal plasma flow was markedly reduced in 1, but remained normal in 2 who had anemia (in anemia the blood flow but not the plasma flow is reduced [236]). Tm_{PAH} was within normal limits in all men except 2 who had hypertensive disease, which may itself reduce this function. The filtration fraction was low on salt, and subsequently increased in 2 patients wh[o] were treated with DCA; this fraction was normal or slightly el[e]vated in all but 1 of the patients who had been maintained wi[th] DCA or cortical extract. Although the C_{PAH}/Tm_{PAH} was low n[or]mal in the patients on salt therapy, those who had been on D[CA]

* The excretory activity of chick proximal tissue in tissue cultures is incre[ased] by whole cortical extract and by compound E, but not by compound A o[r] amorphous fraction. L-Ascorbic acid is also ineffective.[341]

therapy for long periods, or who had pituitary insufficiency, showed a relatively greater reduction of renal blood flow than of Tm_{PAH}. This finding suggests that DCA therapy operated either to maintain Tm_{PAH} or to reduce the effective renal blood flow, perhaps by an adverse action on the renal vascular tree.

From Waterhouse and Keutmann's observations, it appears that the patient with Addison's disease prior to specific therapy will show a low filtration fraction, in contradistinction to panhypopituitarism where the untreated subject may be expected to show a high filtration fraction. None of the functions studied increased consistently under treatment with DCA or cortical extract, and it may be that the treatment was inadequate or that irreversible changes had occurred in the kidneys. In this connection, the sex differences noted above are of interest. The renal blood flow and filtration rate were more markedly reduced in women than in men, and in women Tm_{PAH} was reduced whereas it was normal in 4 men without hypertensive disease. Testosterone propionate failed to restore Tm_{PAH} in women, although the authors recognize that hormonal factors made by the testes appear to maintain a sex difference in Tm_{PAH} in favor of males. However, testosterone propionate is ineffective in increasing tubular function in dogs and man, despite its renotrophic action in rodents (ch. xv).

Repeated administration of ACTH increased the filtration rate, renal plasma flow, and uric acid clearance in 2 patients with hypopituitarism and in 1 patient with lymphatic leukemia, but not in a patient with pernicious anemia.[967]

As Talbott *et al.*[2043] observe, the pathogenesis of depressed renal function in Addison's disease is functional, in the sense that no structural changes are consistently observed in the kidneys of patients who have died of advanced adrenal insufficiency. Nevertheless, the data indicate that some impairment of the vascular tree and tubules of a profound and difficultly reversible nature occurs in chronic disease and, in acute adrenal insufficiency, marked reduction of blood flow, filtration rate, and Tm_{PAH} occur, though possibly entirely because of circulatory insufficiency.

Clinical disturbances of unidentified etiology have been described, in which there is abnormal retention of sodium and chlo-

ride, presumably renal in origin,[41] but the mechanism is wholly obscure.

CUSHING'S SYNDROME

Cushing's syndrome is accompanied by hyperfunction of the adrenal. In such subjects, DCA caused an increased excretion of sodium rather than retention.[1950,1951] When 400 cc. of 5 per cent sodium chloride were given to 3 normal subjects, chloride and water excretion increased slightly during the next 80 min., while in patients with Cushing's syndrome chloride and water excretion were much more markedly increased. The effects of hypertonic saline on the filtration rate and renal plasma flow in both groups were slight and inconstant. The authors incline to the view that in Cushing's syndrome there is increased production of hormones of the 17-hydroxycorticosterone type, which are believed to accelerate the excretion of sodium.

CHAPTER XIII

Acid-base Equilibria in Plasma and Urine

EXCRETION OF ACID

One of the most carefully guarded features of the electrolyte pattern of the plasma is the H^+ ion concentration, which is maintained close to pH 7.4 by the buffering action of the salts of weak acids. Because of its great importance in the neutralization of acids other than H_2CO_3, the plasma $BHCO_3$ is frequently called the 'alkali reserve.' For the neutralization of H_2CO_3 itself the other buffers of the blood and tissues, and chiefly the BHb of the red blood cells, afford a supply of base which is commonly designated as 'total available base.' *

In the plasma, and hence in the glomerular filtrate, all the acid-base components—H_2CO_3, HPr, $H_2PO_4^-$, etc.—are necessarily in equilibrium with the same H^+ ion concentration, and it is improper to say that the latter is determined by any one buffer system. But, in quantity of production and excretion, the H_2CO_3—$BHCO_3$ system is by far the most important. H_2CO_3 is the chief acid formed in the oxidation of food; the quantity produced by a normally active man amounts to over 20 mols/day, equivalent to 2 liters of concentrated HCl or over 20 times the total available

* We may omit the hemoglobin of the red cells from the following discussion, although this constitutes the chief source of alkali for the respiratory transportation of CO_2, and is second only to $NaHCO_3$ in buffering the blood against the invasion of fixed acids, it participates in renal function only indirectly through the plasma, since the kidney cannot operate upon it directly.

base in the body, which may be taken as 1000 mEq. Because of the volatility of its anhydride, CO_2, this acid is excreted almost entirely by the lungs. Thus, in the first instance, the respiratory center is charged with the chief responsibility for regulating the H^+ ion concentration of the plasma by regulating its CO_2 tension. But, according to the mass law, $BHCO_3$* plays stoichiometrically an equal part with H_2CO_3 in determining the H^+ ion concentration, and respiration has no power to regulate the concentration of $BHCO_3$ in the plasma, which is accomplished entirely by the kidneys. So, in the final analysis, the regulation of the H^+ ion concentration of the plasma or, more broadly, of the acid-base equilibria of the body fluids, is much more of a renal than a respiratory problem

Tending to deplete the body of its $BHCO_3$, or more accurately of its available base, are such non-volatile acids (H_3PO_4, H_2SO_4, lactic, β-hydroxybutyric, etc.) as are produced by normal or abnormal metabolism The daily metabolism of 100 gm. of protein produces on the average 60 mEq of sulphate by the oxidation of the protein S, and a quantity of phosphate by the oxidation of protein P, which requires 50 mEq of base for its neutralization to pH 7.4. An additional 50 mEq. of base are required to neutralize the phosphate from 100 gm. of fat containing 10 per cent lecithin. Although most proteins bind considerable fixed base at pH 7.4, and meat contains some $NaHCO_3$, the potential acid exceeds the intake of available base by some 50 to 100 mEq/day. In severe ketosis, an additional burden of 500 mEq. or more of β-hydroxybutyric acid may be added from the incomplete oxidation of fatty acids, half of this acid requiring base for its neutralization at the maximal acidity of the urine (pH 4.5).

A normal man excretes 10 to 30 mEq. of free acid per day, and 30 to 50 mEq of acid combined with ammonia. In diabetic acidosis the free acid may increase to 70 to 150 mEq, and the acid combined with ammonia to 300 to 500 If supplied with adequate urinary buffer, the human kidney can excrete at least 480 mEq of free acid per day In nephritic acidosis the free acid drops to 2 to 20 mEq. and that combined with ammonia to 0.5 to 15 mEq/day.

* The expression $BHCO_3$ is to be preferred to $NaHCO_3$, since any cation may participate in the stoichiometric reactions described here.

2. By forming NH_3 from amide and amino acid precursors. This synthetic cation serves as a substitute for inorganic base in the neutralization of H_2SO_4, BH_2PO_4, etc., permitting the further conservation of B^+ and accounting for the excretion of 20 to 5 mEq. of acid per day, though this figure may reach 500.

The relative importance of these processes in ammonium chloride acidosis is illustrated later in this chapter (fig. 72).

ACIDIFICATION OF THE URINE

The acidification of the urine is accomplished as follows: the glomerular filtrate contains approximately the same concentration of $BHCO_3$ per kg. of water as the plasma, the sole deviation being that due to the Donnan equilibrium; part of this $BHCO_3$ is normally reabsorbed as such in the proximal tubule, the remainder being passed to the distal tubule where the urine is acidified. Here H^+ ions are added by the tubule cells to the tubular urine, with two consequences: (a) the urinary buffers are converted in part (in inverse proportion to pK′) to free acids; and (b) the B^+ ions thus liberated are made available for reabsorption by the tubule cells:

(1) $\downarrow H^+ + BHCO_3 \rightarrow H_2CO_3 \rightarrow CO_2 + B^+\uparrow$

(2) $\downarrow H^+ + B_2HPO_4 \rightarrow BH_2PO_4 + B^+\uparrow$

(3) $\downarrow H^+ + B$ lactate $\rightarrow$ lactic acid $+ B^+\uparrow$

(4) $\downarrow H^+ + BA \rightarrow HA + B^+\uparrow$

The CO_2 formed from $BHCO_3$ is reabsorbed as such by passive diffusion into the tubule cells and is there available to combine with reabsorbed B^+ to form $BHCO_3$, which is then returned to the plasma, the final acidified urine having a CO_2 tension equal to that of the renal venous blood. B^+ liberated from acids other than CO_2 is also reabsorbed with Cl^- to form plasma BCl.

It is to be noted that the two major buffers present in the plasma and the glomerular filtrate, $BHCO_3$ and B_2HPO_4, are themselves subject to elective reabsorption by the tubules. The acidification of the urine therefore presents the circumstance that two or more buffer systems, the acid-base equilibria of which are interde-

pendent because they are contained in the same solution, require more or less independent excretion.

THE ISOHYDRIC PRINCIPLE APPLIED TO PLASMA AND URINE

In accordance with what the physical chemist calls the isohydric principle, all buffers in a common solution are in equilibrium with the same H^+ concentration, and therefore the acid/salt ratio of any one buffer determines this ratio for all other buffers, the respective ratios being in inverse proportion to the dissociation constants of the respective acids:

$$(5) \qquad (H^+) = \frac{(HA_1)}{(A_1^-)} k_1 = \frac{(HA_2)}{(A_2^-)} k_2 = \frac{(HA_3)}{(A_3^-)} k_3 \cdots$$

This equation applies independently to plasma and urine since (H^+) in these two fluids is independent

The important normal buffers common to plasma and urine are H_2CO_3—$BHCO_3$ and BH_2PO_4—B_2HPO_4 (the full list would of course include β-hydroxybutyric acid, acetoacetic acid, certain amino acids, creatinine, etc) and any change in the ratio $(HA)/(A^-)$ for one of these buffers must be accompanied by a simultaneous change in the ratio for all others Since all buffer ratios are dependent on (H^+), the acidification of the urine could theoretically be effected by a tubular operation on any one of the molecular species involved (i e on H_2CO_3, $H_2PO_4^-$, HCO_3^-), or on any two of them, or upon the H^+ ion alone If for example H_2CO_3 and HCO_3^- were reabsorbed (singly or independently of each other, as might be the case) the ratio $(H_2PO_4^-)/(HPO_4^=)$ would be set by the resulting value of (H^+), in accordance with the ratio $(H_2CO_3)/(HCO_3^-)$, or, if the urine were acidified by the addition of (H^+) to a specified concentration, then both $(H_2CO_3)/(HCO_3^-)$ and $(H_2PO_4^-)/(HPO_4^=)$ would be set by this operation

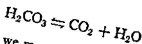
The excretion of HCO_3^- in the urine in either acidosis or alkalosis, and indeed the distribution of this ion between the plasma and any body fluid, presents a unique situation In general, CO_2 penetrates tissues so rapidly (10 times as rapidly as O_2) that the CO_2 tension of two fluids separated by only a thin membrane (as is the case with the tubular urine and plasma) tend rapidly to reach the same value by diffusion.*

* A clear distinction must be drawn here between H_2CO_3 and CO_2 The physical properties of CO_2 are such as to endow it with great penetrating power, whereas in the light of our knowledge of the permeability of living cells to aliphatic acids, it would be inferred that H_2CO_3 would penetrate very slowly, even more slowly than lactic or glycollic acid. In aqueous solutions at equilibrium, 99 9 per cent of the total CO_2 is present as dissolved CO_2 and not as H_2CO_3, and this is probably true of plasma and of tubular urine.

Apart from accidental factors which might retard the attainment of equilibrium, we may take the CO_2 tension of the plasma and urine* to be identical:

(6)
$$(CO_2)_u/(CO_2)_p = 1.0$$

Assuming that the equation

(7)

$$H_2CO_3 \leftrightharpoons CO_2 + H_2O$$

proceeds to equilibrium, we may write:

(8)
$$\frac{(CO_2)}{(H^+)(HCO_3^-)} = k$$

for both plasma and urine, where (CO_2) = the total unionized H_2CO_3 plus free CO_2.

Since k is a constant, the equilibrium concentration of any one of the three species involved is determined by the concentration of the other two species. This is true, with due consideration of thermodynamic activities, for both plasma and urine, and wholly apart from whether one or more of these species is transferred actively or passively from urine to blood, or *vice versa*. It follows that, if the U/P ratios of two of these species are given, for example $(CO_2)_u/(CO_2)_p$ and $(H^+)_u/(H^+)_p$, then the ratio of the third, $(HCO_3^-)_u/(HCO_3^-)_p$, is thereby fixed.

It follows from equations 6 and 8 that, in acidifying the urine, the tubules can operate on H^+ or HCO_3^- ions in the tubular urine, but not independently on both. If the tubules operate on any one of these species, then the ratio $(H_2PO_4^-)_u/(HPO_4^=)_u$ in the tubular urine is automatically set in consequence of equation 6. In view of the statement, to be supported shortly by evidence, that the tubules operate on H^+ ions, it follows that both the absolute value of $(HCO_3^-)_u$ and the ratio $(H_2PO_4^-)_u/(HPO_4^=)_u$ (and of all other buffers) are fixed by the final value of $(H^+)_u$

THE TUBULAR EXCRETION OF H^+ IN EXCHANGE FOR B^+ IONS

Pitts and his coworkers [1833 1636] point out that three theories as to the nature of this process have been proposed. We restate these theories with the additional qualifications imposed by the isohydric principle and the premise that $(CO_2)_u/(CO_2)_p = 1.0$.

* That CO_2 is not actively reabsorbed by the renal tubules is indicated, as Sendroy *et al* [1841] point out, by the fact that the CO_2 tension of the urine is never less than that of the arterial blood.

1. *The phosphate reabsorption theory:* A filtrate containing $HPO_4^{=}$ and $H_2PO_4^-$ in the ratio in which they exist in the plasma (4:1) is formed at the glomerulus. The $H_2PO_4^-$ is excreted, while variable amounts of $HPO_4^{=}$ are reabsorbed by the renal tubules and, reacting with plasma H_2CO_3, reconstitute plasma HCO_3^- and $H_2PO_4^-$.[1597] Here, tubular reabsorption determines the final $(H_2PO_4^-)_u/(HPO_4^{=})_u$ ratio, and, through the isohydric principle, this ratio determines the $(HCO_3^-)_u/(CO_3^{=})_u$ ratio, so that if $(CO_2)_u/(CO_2)_p = 1.0$, the absolute amount of HCO_3^- in the urine is fixed.

2. *The H_2CO_3 filtration theory:* The glomerular filtrate contains HCO_3^- and H_2CO_3 in the ratio of 20:1. This theory treats the renal tubules as impermeable to H_2CO_3 and to CO_2, and presupposes that they actively reabsorb HCO_3^-, the unreabsorbed H_2CO_3 and the amount of HCO_3^- left in the urine determine $(H^+)_u$.[1441] Here the ratio $(H_2PO_4^-)_u/(HPO_4^{=})_u$ is automatically set by $(H^+)_u$, but the absolute amount of phosphate in the urine depends on the reabsorption of $H_2PO_4^-$ and/or $HPO_4^{=}$.

3. *The ionic exchange theory.* Here it is supposed that the tubule cells reabsorb B^+ ions and replace them by H^+ ions by an ion exchange mechanism which operates independently of the associated anions in the urine; as acidification progresses, HCO_3^- is converted into H_2CO_3 and hence into CO_2, which largely escapes by diffusion across the tubules back into the blood.* [1325] The ratios $(H_2CO_3)_u/(HCO_3^-)_u$ and $(H_2PO_4^-)_u/(HPO_4^{=})_u$ are set by $(H^+)_u$, the absolute amount of phosphate is determined by electric tubular reabsorption of one or both phosphate ions; but if

* W. W Smith [1344] has examined the mechanism of acidification in the urine in the dogfish, *Squalus acanthias*. In this animal, as in the marine fishes generally, the pH of the urine is relatively constant (5.7) and uninfluenced by the injection of large quantities of PO_4 (pH 7 4 to 7 7) or $NaHCO_3$. This fixed acidity appears to be an adaptation to the invariable presence in the urine of large quantities of Mg (absorbed by the intestinal tract from ingested sea water), which precipitates as $Mg(OH)_2$ or $MgNH_4PO_4 \cdot 3H_2O$ if the urine is alkalinized beyond pH 6 0. Both endogenous and exogenous PO_4 are excreted by the dogfish tubules and the urine invariably has a high PO_4 content. From observations based on the plasma and urine pH and PO_4 excretion after the administration of PO_4 or $NaHCO_3$, Smith concluded that the most probable mechanism of acidification is the substitution of H^+ for B^+ ions, after and independently of the tubular excretion of PO_4

$(CO_2)_u/(CO_2)_p = 1.0$, the U/P ratio of HCO_3^- and the absolute amount of HCO_3^- excreted in the urine are fixed by the independently regulated terms, $(CO_2)_p$ and $(H^+)_u$.

Any one of these theories is plausible,* but in the first two the maximal quantity of titratable acid which can be *excreted* is limited by the quantity of $H_2PO_4^-$ or H_2CO_3, respectively, contained in the glomerular filtrate. In the third theory, the limit of acid excretion would be determined by the quantity of H^+ ions which the tubules could add to the tubular urine. Although the maximal H^+ ion concentration of the urine is limited to about pH 4.8, the *quantity* of H^+ ions added to the urine (i.e. the maximal quantity of titratable acid) will be conditioned by the presence in the tubular urine of one or more suitable substrate buffers with which the added H^+ ions can react, as in equations 1 to 4 Given adequate substrate buffer, the maximal quantity of titratable acid would presumably be limited only by the maximal rate of H^+ ion exchange.

Pitts and Alexander[1686] have determined the maximal rate of titratable acid excretion during acidosis in the dog, when the urine is enriched with substrate buffer in the form of phosphate or creatinine. They find that this rate is so great that it can be explained only by the third theory, i.e. the tubular exchange of H^+ ions for B^+ ions.

During moderate acidosis, the dog, if supplied with adequate neutral phosphate ($pK' = 6.8$) as a substrate buffer, can excrete

* Montgomery and Pierce[1469] have shown that 0 33 M sodium phosphate solution of pH 7 5, containing phenol red, when retained within the distal tubule of the frog [illegible]

mEq. (or about 80 per cent) of the [illegible]
in 126 out of 227 mEq (or 56 per [illegible]
sorb this quantity of base from the tubular urine in less than 60 seconds, and therefore neither mechanism is beyond the range of possibility But since phosphase is very slightly reabsorbed by the frog tubule when the concentration in the plasma, and hence in the glomerular filtrate, is elevated by only a few mEq., such extensive reabsorption from 0 33 M solution appears unlikely. Therefore the only plausible explanation of the acidification of the urine in the frog is the exchange of H^+ ions for B^+ ions

from 0.198 to 0.431 mEq. of titratable acid * per min., equivalent to 285 to 620 mEq/day, this titratable acid being represented in the urine by $H_2PO_4^-$. As calculated from the rate of filtration, only 17 to 24 per cent of this acid could be accounted for by the H_2CO_3 filtration theory, and only 7 to 11 per cent by the phosphate reabsorption theory The sum of the two glomerular acids ould account for only 24 to 37 per cent of the total acid excreted. Therefore another mechanism must be involved. Since no significant quantity of anion other than substrate buffer (PO_4) is present in the urine under conditions of the experiments, the tubular excretion of a third acid can be excluded and only an ion exchange mechanism is left to account for the acidification process.

Menaker [1483] has pointed out that the reabsorption of B_2CO_3 or BOH from a neutral urine would lead to acidification through the shift in equilibrium between the $CO_3^=$ and HCO_3^- ions, and notes that it is impossible on the present evidence to choose between this mechanism and the H^+ ion exchange mechanism postulated above However, as Pitts [1484] noted in advance of this criticism, the most efficient anion reabsorptive mechanism known, that for HCO_3^-, is capable of 99.99+ per cent removal to a final concentration of 10^{-7} M. The accomplishment of acidification to pH 4 5 by the reabsorption of $CO_3^=$ or OH^- would require that the efficiency of the reabsorptive mechanism be nearly 1000 times that of the HCO_3^- reabsorbing mechanism. In view of the rapidity, in the experiments of Montgomery and Pierce,[1485] with which pure 0 33 M phosphate solution is acidified in the distal tubule of the frog where no $CO_3^=$ ion is available, and in view of the data from comparative physiology on the permanently acid or alkaline state of certain body fluids,[1314,1318] the writer, even though holding the issue *sub judice*, is inclined to favor the H^+ ion exchange mechanism.

Pitts and Alexander chose creatinine ($pK' = 4.97$) as an alternative substrate buffer to phosphate. When the plasma creatinine was elevated to some 200 mg. per cent, the quantity of titratable acid in the urine again reached values (0.099 to 0.146 mEq/min.) far in excess of the quantity of $H_2PO_4^-$ or H_2CO_3 contained in the glomerular filtrate, and an ion exchange mechanism is the only one that can quantitatively account for the facts. The ultimate source

* Titrated from the pH of the urine (3.89 to 6.43) either to that of the arterial blood or arbitrarily to pH 7 35

fering capacity within the possible range of urinary pH. And the more of any buffer the urine contains, the greater the titratable acidity for any value of (H^+) ion gradient (see fig. 65 for data on man).

In parallel experiments, Pitts, Lotspeich, Scheiss, and Ayer[1181] have shown that the acidification of the urine in man follows the

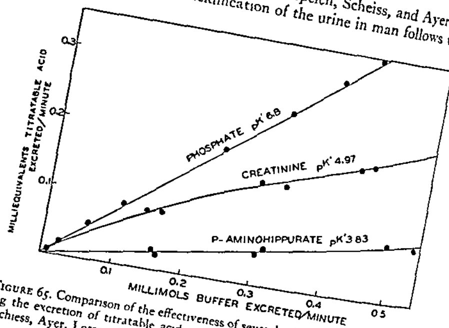


FIGURE 65. Comparison of the effectiveness of several urinary buffers in enhancing the excretion of titratable acid in man in acidosis. All data on 1 subject (Schiess, Ayer, Lotspeich, and Pitts[1181])

same pattern as in the dog. During acidosis induced by the ingestion of ammonium chloride, the excretion of titratable acid far exceeds that which enters the urine in the glomerular filtrate as H_2CO_3 or BH_2PO_4, and, as in the dog, acid must be added to the urine by an ion exchange mechanism, the tubular excretion of preformed acid being excluded by the absence of any residue of such acid in the urine.

In these experiments on themselves, Pitts and his coworkers obtained urine much more acid (pH 4.48 and 4.60) than was observed in the dog, and representing a H^+ concentration gradient between blood and urine of some 800 to 1. Because the minimal pH is lower in man than in the dog, at equivalent rates of buffer ex-

cretion man excretes more titratable acid than does the dog. In one period, one subject excreted acid at a rate of 0.333 mEq/min. (480 mEq/day)—some 3 to 4 times the highest rate ever recorded in diabetic ketosis. This was accomplished only because the plasma phosphate had been elevated to 6.52 mM/liter, thus greatly increasing the substrate buffer available to the tubules. Had the available buffer been further increased, as in the dog experiments, the rate of acid excretion would presumably have increased pro-

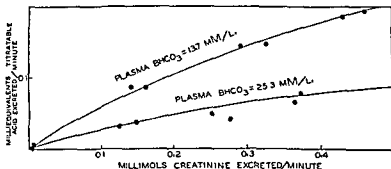


FIGURE 66 The excretion of titratable acid normally and in acidosis in the same subject at a series of comparable excretion rates of creatinine. (Schiess, Ayer, Lotspeich, and Pitts [1781])

portionally. Schiess, Ayer, Lotspeich, and Pitts [1781] have shown that in man, as in the dog, the pK of the buffer is a critical determinant in acid excretion, phosphate, creatinine, and PAH diminishing in effectiveness as buffers in the order named (fig. 65). For any one buffer, the greater the degree of acidosis, the greater is the conversion of that buffer from the salt to acid form, and hence the greater is the quantity of titratable acid excreted (fig. 66).

EXCRETION OF BICARBONATE

In the normal individual, the concentration of $BHCO_3$ in the extracellular fluid is maintained within the limits of 24 to 28 mEq/liter, despite wide variations in the intake of acid- and base-forming foodstuffs As with the sodium concentration of the extracellular fluid, the kidney has the sole responsibility for this regulation.

It has been seen that, during metabolic acidosis, when the individual is faced with a continuous loss of available base in combination with fixed acids, the kidneys conserve base by excreting a mildly acid urine with maximal titratable acidity effected through the normal substrate buffer, phosphate, the bicarbonate of the glomerular filtrate being practically completely reabsorbed. On the other hand, when an alkaline diet is ingested or during metabolic alkalosis, supplies of available base exceed the needs of the body and the excess base is excreted as $BHCO_3$, leading to the formation of an alkaline urine. The urine base in alkalosis always takes the form of $BHCO_3$, whether initially acquired as $BHCO_3$, BOH, or by the oxidation of the inorganic salts of organic acids. The tubular reabsorption of HCO_3 is therefore a physiological process which must be examined in its own right.

The quantitative importance of the problem is evident from the fact that approximately 190 liters of plasma, containing on the average 25 mM. of HCO_3^- per liter and making a total of 4750 mM. of HCO_3^- (or 400 gm. of $NaHCO_3$) are filtered per day. This is roughly 5 times the total available base of the body. Normally a little over 2 mM. are excreted, 99.95 per cent of the filtered HCO_3^- being reabsorbed. But, after the ingestion of $NaHCO_3$ in large amounts, excretion may increase to 1000 mM/day or more. The urine concentration may rise to 220 mM/liter, but since the urine CO_2 tension is never below and, under these conditions, is generally above that of the blood, the urine is never more alkaline than pH 8.0. Thus large quantities of base can be excreted in combination with the chief metabolic acid, CO_2, of which a large excess is always available, in a urine which is only slightly alkaline.

The variable excretion of HCO_3^- in defending the body against alkalosis is therefore complementary to the acidification of the urine in defending the body against acidosis. However, it is possible to speak of two separate processes, the 'acidification of the urine' and the 'reabsorption of bicarbonate,' only in a qualified sense: the evidence indicates that reabsorption of HCO_3^- occurs in two stages, some four-fifths of the filtered HCO_3^- being reabsorbed in the proximal tubule isohydrically, i.e. without change in the H^+ ion concentration of the tubular urine, and one-fifth in the distal tubule anisohydrically. The proximal reabsorption of

HCO_3^- is independent of the acidification process, and may be considered as one which proceeds independently of acid-base balance. In the distal tubule, however, HCO_3^- reabsorption and urine acidification are simultaneous and interdependent; it may be that they represent two consequences of a single process, the exchange of H^+ for B^+.

MAXIMAL TUBULAR REABSORPTIVE CAPACITY

Pitts and his coworkers[1637, 1640] have examined the reabsorption of HCO_3^- in the dog and man by varying the plasma HCO_3^- concentration. Concentrations of HCO_3^- below normal (c.25 mEq/liter) were attained by acidosis induced by the oral administration of NH_4Cl, while plasma levels above normal were attained by the intravenous infusion of $NaHCO_3$.

Figure 67 shows the general relationship between $(HCO_3^-)_p$ and the quantity of HCO_3^- filtered, excreted, and reabsorbed in the dog This figure is based upon 18 experiments in 4 dogs studied by Pitts and Lotspeich,[1640] in which the filtration rate in various experiments ranged from 46 to 101 cc. The data are expressed in mEq. of HCO_3^- per 100 cc of glomerular filtrate, first, for ease of comparison of various animals, and, second, because there is apparently a physiological relation between HCO_3^- reabsorption and filtration rate. As $(HCO_3^-)_p$ increases, the quantity filtered increases in direct proportion; essentially all the filtered HCO_3^- is reabsorbed until the load exceeds 2.5 mEq/100 cc of filtrate, when frank excretion of HCO_3^- begins. The quantity reabsorbed remains constant at this value despite further increases in $(HCO_3^-)_p$, the excess being excreted. Thus there is grossly a maximal reabsorptive capacity for HCO_3^- which is reached at a filtered load of c.2.5 mM/100 cc of glomerular filtrate per min.; i.e. the critical value of $(HCO_3^-)_p$ required to cause frank HCO_3^- excretion is about 25 mEq/liter (though different animals showed some variability in this figure).* The corresponding figure in three

* This value is influenced in the dog to a slight extent by water diuresis, which tends to increase the HCO_3^- excretion, and by the concentration of total body electrolytes and their specific pattern; depletion of Cl^- tends to conserve HCO_3^- and substitution of K^+ for Na^+ may alter the critical value of $(HCO_3^-)_p$ at which excretion begins.

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men studied by Pitts, Ayer, and Schiess [1637] is 28 mEq/liter (fig. 68).

It is to be noted that uniformity in reabsorption of $BHCO_3$ in the same animals or in different animals with widely varying

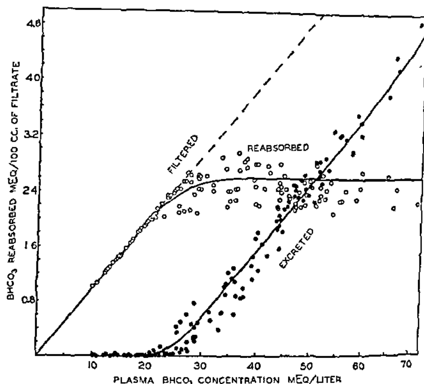


FIGURE 67. The excretion of bicarbonate in the dog as a function of plasma concentration. Note that the quantities reabsorbed and excreted are expressed in mEq/100 cc of glomerular filtrate (Pitts and Lotspeich [1640])

filtration rates is achieved only when the amount reabsorbed is expressed per 100 cc. of filtrate. This implies that (proximal) tubular reabsorptive capacity is functionally related to the filtration rate,* as is the case with sodium chloride.

* The comparison of data on any aspect of renal function in different animals per cc. of filtrate obviously tends to eliminate differences attributable to renal size. Thus, there normally exists a close correlation between the filtration rate and glucose Tm on the one hand or diodrast Tm on the other, not only between different individuals but in individual nephrons,[1939] a correlation which has its

In the frog, *Necturus*, and rat, ultimate acidification of the urine occurs in the distal tubule (ch. II). That some reabsorption of HCO_3^- occurs in the proximal tubule is plausible in view of the proximal reabsorption of sodium chloride and water. Since the pH of the urine at the end of the proximal tubule is practically identical with that of the glomerular filtrate, proximal reabsorption must be an essentially isohydric process. When the bladder urine

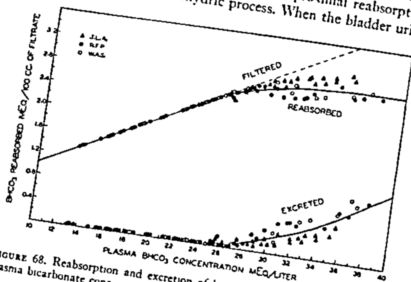


FIGURE 68. Reabsorption and excretion of bicarbonate in man in relation to plasma bicarbonate concentration (Pitts, Ayer, and Schiess 1407)

is acid (i.e. in acidosis), the remainder of the HCO_3^- must be reabsorbed (or removed by acidification) distally, the process coinciding with the process of acidification.

Pitts and Lotspeich infer that proximal reabsorption accounts for roughly four-fifths, and distal reabsorption one-fifth of total reabsorption. This division is based upon the evidence previously

genesis in morphological balance. Comparisons per unit of filtrate are valid for establishing a *functional* relationship only where it can be shown that the variable under consideration increases or decreases with the filtration rate in individual animals. Pitts and Lotspeich's data seem to establish this as the case of the maximal reabsorptive capacity for HCO_3^-. In this respect, the reabsorption of HCO_3^- differs from that of glucose, vitamin C, phosphate, and sulphate, which is independent of the filtration rate.

cited that such is roughly the division of sodium and water reabsorption.

Two lines of experimental evidence in the dog support this view. Sulfanilamide reduced the capacity of the kidney to reabsorb HCO_3^-, at both normal and increased HCO_3^- loads. However, the depression of reabsorption was small in either circumstance, indicating that the greater fraction of the reabsorptive process involved a non-sulfanilamide-sensitive mechanism. Since, as stated above, sulfanilamide also depressed the distal acidification mechanism, Pitts and Lotspeich infer that the depression of HCO_3^- reabsorption effected by sulfanilamide represents distal reabsorption, and the sulfanilamide-insensitive process is therefore attributed by inference to the proximal tubule.

Secondly, when HCO_3^- is administered to an acidotic dog enriched with phosphate as a substrate buffer, the titratable acidity of the urine decreases as the quantity of filtered HCO_3^- increases, even though all the filtered HCO_3^- is reabsorbed. This can be explained by the supposition that some of the HCO_3^- reaches the distal tubule, and there competes with phosphate for H^+ and diminishes the extent to which $HPO_4^=$ is converted to $H_2PO_4^-$, thereby reducing the titratable acidity. Consequently, Pitts and Lotspeich conclude that the final reabsorption of HCO_3^- is accomplished by the same mechanism which, by the H^+ exchange, acidifies the urine. This process is independent of the filtration rate but, being small in magnitude (one-fifth of total reabsorption), it has little effect upon the picture presented by total reabsorption.

It is proximal reabsorption which is functionally related to the filtration rate. In order to explain this functional relationship, Pitts and Lotspeich conceived that the proximal reabsorption of HCO_3^- and of water could be treated as simultaneous and related processes, so that one could speak of a maximal concentration of HCO_3^- in the 'proximal reabsorbate.' They posited that this maximal concentration is 25 mEq/liter (the normal concentration of HCO_3^- in dog plasma). If this 'proximal reabsorbate' always represents four-fifths of the water of the glomerular filtrate, and if the concentration of HCO_3^- in this reabsorbate is limited to a value of not more than 25 mEq/liter, then the quantity of HCO_3^- so reabsorbed will of course vary roughly in proportion to the

filtration rate (fig. 69). But why the concentration of HCO_3^- in the proximal reabsorbate should be limited to 25 mEq/liter is not stated, and the postulate can be shown to be untenable * by the fact that, during osmotic diuresis induced by mannitol or urea, some 65 per cent of the water of the glomerular filtrate may be carried into the urine without significantly decreasing HCO_3^- re-

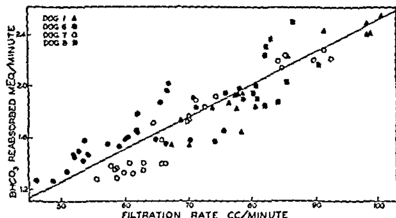


FIGURE 69 Reabsorption of bicarbonate in the dog as a function of the filtration rate All observations were made at plasma bicarbonate concentrations well above the renal threshold The filtration rate in each animal was varied by fasting and by feeding meat. (Pitts and Lotspeich [1640])

absorption.[1458, 5171] HCO_3^- reabsorption continues whether water is reabsorbed or not (see fig. 55).

Pitts *et al.*[1457] note that HCO_3^- appears to be reabsorbed in the proximal tubule ahead of or more rapidly than chloride (p. 31),



break down during elevation of plasma bicarbonate concentration, or no such limitation can apply The most satisfactory solution is to reject the limitation in concentration in the proximal reabsorbate which at this time seems artificial since no simultaneous HCO_3^- plus water reabsorbate can be visualized

carry weight only if it is assumed that the rate of secretion of H^+ is limited and essentially the same in acidosis and in alkalosis To the maximal rate of acid excretion reached in man (0.333 mEq/min.) (and this figure is set only by the available substrate buffer) must be added the HCO_3^- which is simultaneously neutralized, so that the true maximal rate of H^+ ion exchange must considerably exceed the supposed 0.5 mEq/min. of HCO_3^- reabsorbed during alkalosis. If the two operations represent an identical process of H^+ ion exchange, it is impossible on the data to limit that process by a maximal rate.

It is, however, a tempting hypothesis to accept that the distal reabsorption of HCO_3^- reflects not the operation of a specific mechanism but merely an incidental consequence of the secretion of H^+ ions. Against this view, however, is the fact emphasized by Pitts and his coworkers, and upon which the investigations above throw no light, that alkalosis induced by hyperventilation causes increased bicarbonate excretion without elevation of plasma HCO_3^-. Forced breathing, induced voluntarily or reflexly in consequence of anoxia, lowers the bicarbonate concentration of the blood but paradoxically leads to the formation of alkaline urine. Obviously the activity of the renal tubules in reabsorbing HCO_3^- must here be reduced by changes in the pH of the plasma or by other means. It is difficult to reconcile the continuous secretion of H^+ in the distal tubule with the alkalinization of the urine under these conditions. Until this phenomenon is assimilated into the theory, and until limitations in proximal reabsorption of HCO_3^- are further clarified, our theory of the excretion of HCO_3^- is obviously incomplete and subject to serious revision.

RELATIONS BETWEEN BICARBONATE AND CHLORIDE EXCRETION

It has previously been noted that Cl^- and HCO_3^- are, within wide limits, substituted for each other in maintaining the total base of the plasma. Thus, in alkalosis produced by protracted vomiting, plasma Cl^- may be low and HCO_3^- correspondingly high; conversely, in acidosis produced by diarrhea, plasma HCO_3^- may be low and Cl^- high

Pitts and Lotspeich [1640] find that, when NaCl is infused in such excess that frank excretion of Cl^- occurs, there is a simultaneous increase in excretion of HCO_3^-, owing to decreased tubular reabsorption, while infusion of HCO_3^- in such excess that frank excretion of this anion oc-

curs, leads to an increased excretion of Cl^- owing to decreased tubular reabsorption; while Pitts, Ayer, and Schiess [1197] in their observations on man report a close reciprocal relationship during acidosis and alkalosis: when the HCO_3^- reabsorbed increased from 1 34 to 2.79 mEq/100 cc of glomerular filtrate, the Cl^- reabsorbed decreased from 10 37 to 9.14 mEq, the sum remaining within the range of 11.71 to 12.70 mEq

However, when the body is depleted of sodium, an acid urine is excreted despite alkalosis. Failure of sodium excretion somehow arrests excretion of both Cl^- and HCO_3^-, and the pH of the urine falls toward that of a solution of free CO_2 Sodium chloride infusions restore HCO_3^- excretion by restoring the underlying disturbances, whereas the infusion of HCO_3^- does not correct these disturbances but, on the contrary, may lead to excessive alkalosis and tetanic convulsions.[2109]

In the absence of data on the filtration rate in such circumstances, one can only speculate on the interpretation, but it is possible that the decrease in filtration rate is enough not only to prevent sodium excretion, but to prevent a significant quantity of HCO_3^- from reaching the distal tubule, and, in absence of HCO_3^- distally, the urine approaches maximal acidity Interest in the point is enhanced by the circumstance that in most, if not all, oligurias (shock, post-transfusion reaction, crush syndrome, carbon tetrachloride intoxication, etc) the oliguric urine is reported to be acid by routine tests.

Wolf [2233] describes the effects of administering potassium chloride, sodium chloride, and water on the pH of the urine Water diuresis consistently causes the pH to shift from the range of 5 0 to 5 5 to the range of 6 0 to 7 0, and Eggleton [511] has shown that the intravenous administration of hypertonic sucrose or sodium sulphate solutions results in an increased acidity but decreased excretion of titratable acid, urea being without this effect in her experiments

THE CO_2 TENSION OF THE URINE

It has frequently been observed that the CO_2 tension of urine removed promptly from the bladder in such a manner as to prevent loss of CO_2 may be several times as great as that of venous blood. This fact led Sendroy, Seelig, and Van Slyke [1891] to suggest that the renal tubules are relatively impermeable to CO_2 However, in view of the experimental refutation of the 'carbonic acid theory' of urine acidification and the *a priori* improbability of any significant degree of impermeability, we may suppose that the tubular epithelium is neither more nor less permeable to CO_2 than are other cells

Occasional high CO_2 tensions in bladder urine can be explained either

as a result of admixture of acid and alkaline urine in the bladder, the result of delayed conversion of H_2CO_3 to CO_2 in the tubular urine,

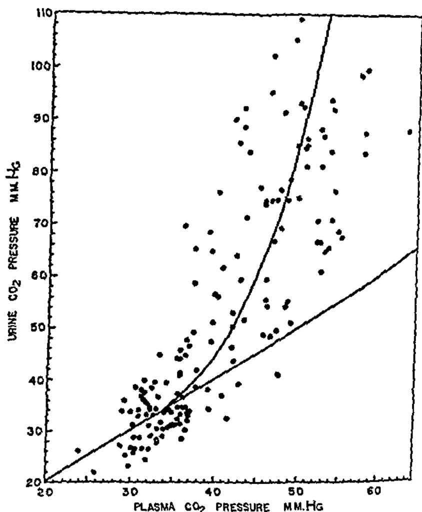


FIGURE 70. The relationship between the partial pressure of carbon dioxide in arterial plasma and in urine collected simultaneously. The diagonal straight line indicates equivalence of partial pressure. The curve is the average of all points, fitted by inspection (Pitts and Lotspeich [1040])

which is lacking in carbonic anhydrase, or the failure of CO_2 to diffuse out of the tubular urine because of the velocity of flow. The second explanation seems the most likely.

Pitts and Lotspeich[140] report that among 160 urine samples in the dog, with pH ranging from 4.96 to 7.96, $(HCO_3^-)_u$ from 0.08 to 197 mM/liter, urine pCO_2 from 22 to 109 mm. Hg, and arterial plasma pCO_2 from 25 to 64 mm. Hg, the relationship between (HCO_3^-) and pH was a uniform one and approximated that demanded by the mass law, assuming a constant renal venous pCO_2 of 50 mm. Hg. There were, however, significant deviations, below pH 7.4 an assumed pCO_2 of 50 mm is too high, and above pH 7.6 it is too low. In acid urines, formed when plasma HCO_3^- is subnormal and the quantity of HCO_3^- delivered to the distal tubule is minimal, the urine pCO_2 is low and tends to approximate the arterial pCO_2; assuming that urine pCO_2 = renal venous pCO_2, this could mean that in acidosis the renal venous pCO_2 is essentially the same as arterial pCO_2, i e most of the CO_2 produced metabolically by the kidney as well as by acidification of the urine is added to the renal venous blood not as CO_2 but as HCO_3^- in association with reabsorbed B^+. However, in alkaline urines formed when the plasma HCO_3^- is above normal and the quantity of HCO_3^- delivered to the distal tubule is considerably increased, the urine pCO_2 exceeds the arterial pCO_2 by a considerable amount (fig. 70), and no doubt exceeds the renal venous pCO_2 This could mean that, in the face of the distal conversion of large quantities of HCO_3^- to H_2CO_3 and in the absence of carbonic anhydrase in the tubular urine, substantial quantities of H_2CO_3 escape reabsorption and appear in the bladder urine.

The data on man[147] agree wholly with those on the dog The urine pCO_2 at low levels of HCO_3^- reabsorption (acidosis) has a value of 30 to 40 mm Hg (i e close to that of the plasma from which it is formed), during abundant bicarbonate excretion, the value rises to as high as 136 mm Hg when pCO_2 in the plasma ranges from 32 to 42 mm. Hg

Ryberg,[148] reporting similar relations between the CO_2 tension and pH of the urine, confirms the conclusion that the H^+ ion exchange mechanism converts bicarbonate to CO_2 during the excretion of an alkaline urine, and that the delay in the dehydration of H_2CO_3 permits considerable quantities of this molecular species to pass into the bladder urine.

THE EXCRETION OF AMMONIA

Ammonia is a relatively toxic substance if injected directly into the venous stream, for under these circumstances it reaches the central nervous system upon which it has a strong convulsive action. Comparatively large doses may be given intra-arterially, however, because it is removed and bound by the tissues When

taken *per os* its toxicity is equally low because it is carried by the portal circulation to the liver where it is converted to urea, this conversion being so efficient that there is no appreciable elevation of the ammonia content of the systemic blood, and it is impossible to increase ammonia excretion directly by the oral administration of ammonium salts. The one circumstance evoking increased ammonia excretion is acidosis, where the ammonium ion serves as a synthetic cation to replace sodium in the urine. The normal individual excretes 30 to 50 mEq/day of ammonia in conjunction with the excretion of sulphate, phosphate, and other fixed acids. A diabetic in severe acidosis may, however, excrete more than 10 times this amount.

In 1921, Nash and Benedict demonstrated that urinary NH_3 is formed in the kidney, and these investigators and others inferred that it is formed from urea, but Pitts [1627] showed that the difference between the urea clearance and creatinine clearance in the dog, a difference which is fairly constant at a given urine flow under all normal conditions, is unchanged as between extreme acidosis and alkalosis; and that, if the nitrogen clearance in acidosis is calculated on the sum of the urea plus ammonia, it may exceed the filtration rate by a considerable amount, whereas the clearance calculated on urea alone maintains its normal value relative to the filtration rate. Pitts concluded that the precursor of ammonia is not urea that has entered the tubular urine by way of the glomerulus. Conceivably, unfiltered urea might be removed from the postglomerular blood and be converted to ammonia by the tubules but it is just as reasonable *a priori* to suppose that the ammonia is formed from some other precursor. Pitts' observations were confirmed by Alving and Gordon,[46] who studied the extraction ratios of creatinine and urea, as well as the clearance ratios, in dogs with explanted kidneys. They found that the relative values of the extraction ratios remained unchanged as between the normal and the acidotic state; hence estimates of the renal blood flow based on the excretion rate and extraction ratio of urea alone gave identical results with estimations based on creatinine, as is the case in the normal animal, whereas such estimates based on the excretion rate of urea plus ammonia gave excessively high figures for the renal blood flow.

Van Slyke *et al.*,[2077] extending the experiments of Alving and Gordon on the dogs with explanted kidneys, confirmed the conclusion that all the urea, as well as all adenosine and adenylic acid, extracted by the kidneys, is excreted as such in the urine. Moreover, inadequate α-amino nitrogen is extracted to provide nitrogen for the ammonia excreted. The amide nitrogen of glutamine, however, is removed from the blood in much greater amounts than appears in the urine, and the excess suffices to provide both the ammonia carried away from the kidney by the renal vein and 60 per cent or more of that which is excreted in the urine. The rest of the ammonia (40 per cent) can be accounted for by the disappearance of α-amino nitrogen. Administration of glutamine to a dog in acidosis markedly increases ammonia excretion, while the amount of glutamine removed from the renal blood is reduced in alkalosis. A glutaminase present in kidney tubules catalyzes the degradation of glutamine to glutamic acid and ammonia.*

Lotspeich and Pitts[1171] have shown that glycine, DL-alanine, L-leucine, DL-aspartic acid, and casein hydrolysate increase the rate of ammonia excretion in the acidotic dog. L-arginine, L-lysine, and L-glutamic acid are without such effect. The capacity of these amino acids to increase ammonia excretion correlates with their susceptibility to oxidative deamination *in vitro* by renal amino acid oxidases, and indicates that such amino acid oxidases are concerned in the syntheses of ammonia by the tubules. There is also a correlation between the capacity of the kidney to use an amino acid for ammonia formation and the capacity of the renal tubules to reabsorb it, possibly because oxidative deamination is involved in both processes. However, this correlation does not imply that the amino acid which is reabsorbed is that which is deaminized to form urinary ammonia; the quantity of amino nitrogen reabsorbed always greatly exceeds that which is utilized in ammonia synthesis.

* According to Archibald[illegible] and Hamilton[illegible] glutamine nitrogen constitutes 18 to 25 per cent of the total free amino acid carboxyl nitrogen of plasma. Its concentration is not appreciably affected by acidosis, alkalosis, or chronic renal disease. The glutaminase content is reduced in chronic renal disease and P... infers that depletion of renal enzymes concerned with ammonia excretion i... basic factor in the incapacity of subjects with chronic glomerulonephritis ... form adequate amounts of ammonia.

Ammonia excretion, like the excretion of acid, is a function of *the last two-thirds of the distal tubule* (and possibly the collecting ducts) in the amphibian kidney,[1469 2130] and it is assumed that ammonia is formed in the distal system in mammals *

Sartorius, Roemmelt, and Pitts[1771] have shown that increased ammonia excretion is demonstrable within a few minutes after the establishment of acidosis, but maximal excretion is not reached for some hours or days. These authors conceive that the stimulus to increased ammonia excretion is the same as that which leads to *acidification of the urine, namely reduction in the quantity of bicarbonate* delivered to the distal tubule, which of course issues from a reduction of the plasma bicarbonate concentration during acidosis. They speak of the distal formation of ammonia as a more or less continuing affair; when the urine is alkaline the ammonia is not captured in the urine but escapes into the blood, an interpretation which would account for the fact, demonstrated by Nash and Benedict, that the ammonia content of renal venous blood is *greater than that of the arterial blood. But*, as the urine becomes acid, the ratio of bound to free ammonia rises (the pK_a' of ammonia is 9.3) and this circumstance promotes its capture by neutralization in the tubular urine. Sartorius, Roemmelt, and Pitts[1634] find that ammonia excretion increases regularly with decreasing urine pH (fig. 71), a fact which they refer to the diffusion of free ammonia from the site of formation in the tubule cell to that of low concentration in the urine, where it exists not as free ammonia but as ammonium ion. It is obvious, however, that some factor other than plasma bicarbonate concentration (and urine pH) conditions the final rate of ammonia excretion, for this continues to increase *after plasma bicarbonate has reached its lowest and steady level* in acidosis, and the acidotic dog excretes more ammonia at the same urine pH than does the normal dog. The degree and duration of acidosis somehow increase ammonia production *in the distal* tubule. The nature of this adaptive factor is unknown.

Ryberg[1755] finds that in man ammonia excretion during acidosis reaches its maximal intensity only after some days and continues

* The kidney of a two-month-old infant who had exhibited signs of acidosis from birth showed necrosis and calcification of the distal convoluted tubules and collecting tubules The glomeruli and proximal tubules were normal.[1194]

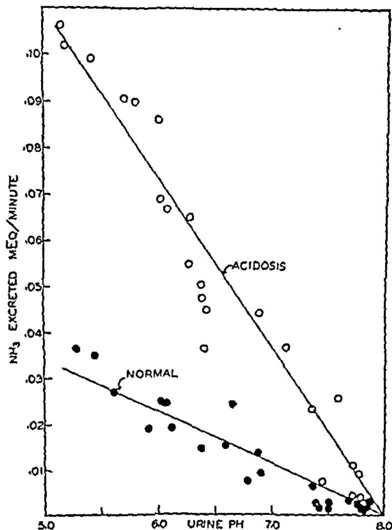


FIGURE 71 The excretion of ammonia in relation to urine pH in a normal dog and in a dog rendered acidotic for 48 hr. (Pitts[199])

for some time after cessation of acidosis. He reports that in dogs, however, ammonia formation reaches its full magnitude in a few hours (in contradiction to Sartorius *et al.*). The rate of production appeared to reach a maximum equivalent to 0.0022 and 0.0024 mEq/cc. of urea clearance in two male subjects and 0.0025 and 0.0024 in two dogs.*

Whereas Pitts and his coworkers think of the secretion of ammonia as simple diffusion of NH_3 from the tubule cell into the urine, Ryberg [1757] finds a positive correlation between ammonia excretion in acidosis and sodium excretion, and he infers that NH_4^+, like H^+, is secreted by exchange for Na^+. A more comprehensive examination of the variables involved is required before selection between these interpretations can be made.

PHYSIOLOGICAL RESPONSES TO ACIDOSIS

Sartorius, Roemmelt, and Pitts [1771] have followed the sequence of changes in the electrolyte pattern of the plasma in man during the development of acidosis following the ingestion of ammonium chloride (fig. 72). Immediately upon absorption, the ammonia of the ammonium chloride is converted to urea, and the liberated hydrochloric acid reacts with sodium bicarbonate to form sodium chloride, the CO_2 being excreted by the lungs. In principle, plasma bicarbonate must decrease and plasma chloride rise, mEq. for mEq., as this conversion proceeds, the plasma sodium concentration remaining unchanged. So far as the kidney is concerned, the relative quantities of sodium and water reabsorbed by the tubules remain grossly constant; the sodium in the reabsorbate must be matched by the sum of the chloride and bicarbonate reabsorbed, and, *since the chloride:bicarbonate ratio in plasma, and hence* in the glomerular filtrate, is increasing in favor of chloride as bicarbonate is reduced, this ratio also increases in the reabsorbate with the result that the plasma chloride increases as bicarbonate depletion progresses But exactly the same initial change in plasma composition would have occurred had the kidneys been removed from the picture entirely.†

However, the substitution of chloride for bicarbonate is attended ini-

* The writer has recalculated these ratios; if he understands correctly, Ryberg gives mEq NH_3 per 24 hr per urea clearance in cc/min.

† The authors emphasize the increased reabsorption of chloride as a specific renal compensation leading to elevation of the plasma chloride, but so long as the sodium:water ratio in the reabsorbate remains constant, the results can be no other than above· the maintenance of a constant plasma sodium concentration and exchange of plasma chloride for bicarbonate.

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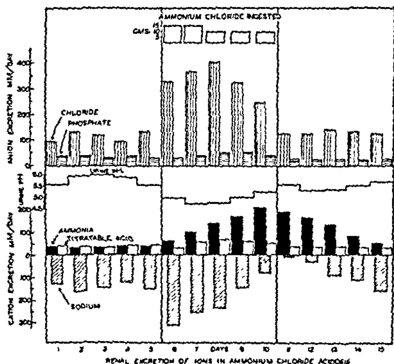


FIGURE 72 Renal excretion of ions in ammonium chloride acidosis (Pitts [304])

though this were the specific effect, but it is equally plausible to believe that it is the reabsorption of sodium that is impeded, resulting in an increased excretion of both sodium and chloride. However, this sodium carries with it nearly equivalent quantities of water, so that progressive reduction of the extracellular fluid occurs, with some simultaneous loss of the intracellular base and excretion of potassium. This latter process permits the body to draw on the large intracellular reserve of base and to curtail the reduction of extracellular volume.

Up to this point, the response of the kidney, with the exception of the transient increase in excretion of sodium, has been treated as though

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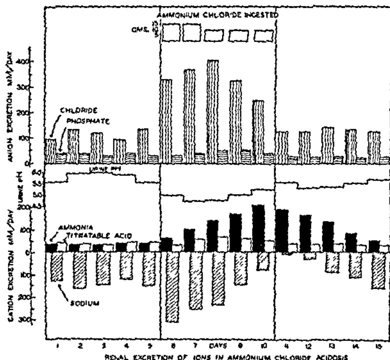


FIGURE 77 Renal excretion of ions in ammonium chloride acidosis (Pitts[1484])

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pensation perhaps reflects the slow regression of ammonia formation in the distal tubule, a process which has been activated by acidosis beyond its normal level.

In the sequence of recovery from acidosis of mild degree, there are apparently no consistent changes in renal plasma flow or filtration rate, the changes in urine composition being referable entirely to tubular kinetics. In extreme acidosis, where dehydration is marked, glomerular activity may be seriously reduced and contribute to the picture by reducing the quantity of substrate buffer delivered to the distal tubule and by reducing the filtered load of sodium.

Ammonium chloride has long been used to force the excretion of sodium and water in edema, on the grounds that conversion of the ammonia to urea liberates chloride, which requires sodium for its excretion This is true only in the first few days, before ammonia excretion has reached its maximal rate. Thereafter, the ammonium ion excreted distally is sufficient to meet the requirements of chloride excretion, and sodium excretion regresses to control levels The natriuretic effect of acidosis is therefore self-limited. To judge by the data of Sartorius, Roemmelt, and Pitts, ammonium chloride acidosis promotes the excretion of more potassium in the first five days than of sodium This fact, coupled with the circumstance that the excretion of fixed base is forced only in proportion to the severity of the acidosis, may account for the waning popularity of ammonium chloride as a diuretic agent, and for *the clinical experience that it is most effective if used for a few days* only at intervals of a week or so

The excretion of the thiosulphate ion is obligatory, and consequently the administration of ammonium thiosulphate should lead, by the conversion of the ammonia to urea, to the obligatory excretion of sodium thiosulphate, or its derivative, sodium sulphate Experiments along this line have been carried out on dogs by Franklin, Genest, and Newman.[487] When a single dose is administered intravenously, about one-fourth is oxidized to sulphate, but, when administered as a single dose orally, half is oxidized to sulphate Since 1 thiosulphate ion on oxidation yields 2 sulphate ions, the potential base-removing power of thiosulphate is doubled by the conversion. In either case, the rapid excretion of single doses is accompanied by a large increase in sodium excretion and a slight increase in potassium excretion However, with repeated doses, acidosis develops as usual and larger amounts of ammonia are excreted, reducing the excretion of sodium and defeating the use of the salt as a sodium remover After single doses the excretion of chloride and phosphate is very low, but with repeated doses there is a low excretion of chloride

it were only continuing its normal operations. This, of course, is only a partial statement. With the induction of acidosis the composition of the urine shifts uniquely by an increase in titratable acidity and an increase in ammonia content.

Sartorius *et al.* explicitly state that the H^+ exchange mechanism of the distal tubule is limited in capacity (*meaning mEq/min*) *and that* the acidification mechanism is identical with the mechanism for the reabsorption of bicarbonate; it is implicit in their view, though not stated *as such, that the* H^+ *exchange mechanism is operating all the time at* full capacity. So long as excess bicarbonate reaches the distal tubule the H^+ exchange mechanism is overloaded, and excess bicarbonate over and above that reabsorbed by acidification is excreted in the urine As the plasma bicarbonate decreases, however, the distal load of bicarbonate falls short of the distal H^+ transfer capacity, and the urine is acidified. Titratable acid is now formed by the acidification of phosphate and other buffers in proportion to the quantity of buffer present and in *accordance with the pK' of these buffers.*

Given an adequate quantity of substrate buffer, the quantity of titratable acid formed would increase in direct proportion to the reduction in distal bicarbonate load (or roughly to the reduction in total plasma bicarbonate) were it not for the excretion of ammonia. Progressive acidification of the urine leads to progressive capture of ammonium ion in the urine, so that considerable chloride (or other strong acid) is now excreted paired with this ion, and sodium is liberated for recombi*nation* with carbon dioxide to form bicarbonate. Thus, in the face of a continuing acidotic liability, increased ammonia excretion plus increased titratable acidity bring the body into a steady state where no further *sacrifice of plasma bicarbonate occurs*

On removal of the acidotic liability, the system operates automatically to restore the plasma bicarbonate concentration; each mol of free acid or ammonia excreted makes available a mol of base for *recombination* with carbon dioxide to form bicarbonate, this process continuing until the increase in plasma bicarbonate concentration leads to the excretion of a neutral urine, without either free acid or significant *quantities of ammonia.*

During recovery, potassium and phosphate are restored to the intracellular compartment and consequently the plasma concentration and excretion of these substances are temporarily reduced below normal Sodium *reabsorption, for reasons unknown,* is accelerated, and the plasma sodium concentration rises slightly above normal, accompanied by a slightly supernormal plasma bicarbonate concentration. This overcom-

Part III

and a marked increase in phosphate excretion. Continuous administration for 6 hr. causes death with a low serum sodium and a high serum potassium. Apparently dilution of the extracellular fluid by loss of sodium leads to a shift of water into the muscles and a shift of potassium from the muscles into the plasma until the concentration of this ion, superimposed on hemodilution, reaches lethal proportions.

CHAPTER XIV

The Control of the Renal Circulation and the Action of Pharmacodynamic Agents

HISTORICAL SKETCH

This chapter in renal physiology begins with Claude Bernard's observation (1859) that, when the splanchnic nerves in an anesthetized animal are sectioned, there results an increased urine flow on the operated side. Bernard had himself discovered the vasomotor nerves and had observed the vasodilator effects of sectioning the vasomotor nerves to the rabbit's ear, and he attributed this diuresis to increased renal blood flow. His conclusion is admittedly correct, but his experiment was unfortunate in two respects. His reasoning in gauging renal blood flow by urine flow was, as we can now see, unsound, during periods of hypotension or extreme renal ischemia there is a general parallelism between the two because cessation of filtration is accompanied by anuria or oliguria, but under normal conditions renal blood flow and urine flow are unrelated. Secondly, the phenomenon of 'denervation diuresis' is observable only under the abnormal conditions of his experiment, which are such as to excite vasoconstriction in the kidney. Important as was his demonstration of the renal vasoconstrictor nerves, Bernard's experiment has persisted in confusing renal physiology to the present day

An extensive literature on renal blood flow, accumulated in the period between 1859 and 1939, has been reviewed elsewhere [1929] and it will suffice if we summarize here only the more important facts emerging from these earlier studies. In 1883, Cohnheim and Roy devised the 'oncometer,' a hollow shell designed to record changes in kidney volume, and

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with it demonstrated that when the splanchnic nerves were sectioned in the anesthetized animal there occurred an increase in renal volume; conversely, the renal volume decreased on stimulation of the peripheral stump of the cut splanchnic nerves. In the main, they were probably correct in attributing the changes in kidney volume to changes in volume of the renal vascular bed, though this is not unconditionally true. Bradford, a pupil of Gaskell who was an authority on the autonomic nervous system, used the oncometer in 1889 to examine the distribution of vasoconstrictor nerves in the mammal. He showed that in the dog these nerves leave the cord in all segments from T4 to L2, being most abundant in the last three thoracic segments, which in the dog would be T10, T11, and T12. (For the finer distribution of vasoconstrictor nerves in the splanchnic tracts, see Gruber[879] and Mitchell.[1455])

In 1893 Landergren and Tigerstedt applied the Ludwig stromuhr to the measurement of the renal blood flow, but they inserted this device in the renal artery and thus traumatized the renal nerves. It remained for Burton-Opitz and Lucas (1908) to modify the Ludwig stromuhr and to insert it in the renal vein so that the circulation of the kidney and its nerve supply would be impaired to a minimal extent. By this more reliable method, Burton-Opitz and Lucas confirmed the function of the vasoconstrictor fibers to the kidney and added various observations on reflex excitation of these tracts. They demonstrated further that the renal innervation was unilateral, and in 1916 Burton-Opitz made the notable observation that a denervated kidney may undergo vasoconstriction in consequence of an increased secretion of adrenalin when the contralateral splanchnic nerve is stimulated.

In 1927 Rein introduced the thermostromuhr, an instrument that, with similar devices described by others,[978, 1095, 1146, 1767] represents the acme of mechanical ingenuity as applied to a difficult problem. However, a physiological disadvantage is still inherent in all stromuhr methods in that the renal vein, the renal artery, or the aorta must be dissected free and enclosed within a device of some weight; there are other minor difficulties such as the calibration of the instrument and the fact that the accumulation of fluid or scar tissue may impair the calibration. But the most uncertain feature of many thermostromuhr experiments lies in the technique of the investigator, for too frequently this involves acute experiments on anesthetized and laparotomized animals, in many instances after excessive physiological insult. Investigators naively revealed that their preparations had to be abandoned because 'no urine was formed by the operated kidney,' or because the renal blood flow was 'abnormally low,' or the renal vascular bed 'no longer responsive.'

In 1936 Mason, Blalock, and Harrison [1415] introduced a venous sound that could be inserted in the jugular vein of a dog and passed into the vena cava; by two expansible balloons carried near the end, the vena cava could be occluded above and below the renal vein while blood from the renal vein itself was being collected.

In 1931–33 H L. Sheehan and his coworkers [658, 1097] first used the extraction ratio of urea and phenol red in an attempt to evaluate the renal blood flow in anesthetized animals. In 1934 Rhoads [1703] described a method of explanting one or both kidneys beneath the skin in dogs so that the renal blood flow could be measured by means of extraction ratios and clearances in the conscious animal, a technique requiring only the simultaneous puncture of the renal artery (or a systemic vein) and of the renal vein in an interval during which the urine was accurately collected This method has been slightly modified by Sheehan [1873] and Page and Corcoran,[1567] and in the hands of numerous investigators it has yielded valuable information on extraction ratios, the renal circulation, and oxygen consumption

In 1941 Cournand and Ranges [438] perfected the technique of catheterization of the right heart in man for the determination of the cardiac output by the direct Fick method Venous catheterization has subsequently been extended to the collection of hepatic and renal venous blood in man, thus making possible the measurement of hepatic and renal extraction ratios, and it may be anticipated that venous catheterization in the dog will to a great degree replace the explanted kidney.

The span of 50 years from the work of Bernard to that of Burton-Opitz and Lucas may be set apart as a pioneer period in renal physiology. In the light of present-day knowledge, certain criticisms may be leveled against the methods used by these investigators but not against the investigators for using them. Their choice of methods and the conduct of their experiments conformed with the knowledge of their time. It is to be regretted that this cannot be said of investigators in the next three decades, many of whom failed to keep their methods and their physiological approach abreast of rapidly developing knowledge.

It was in 1895 that Oliver and Shafer demonstrated the powerful vasomotor properties of extracts of the adrenal medulla, properties that we now know are attributable to the hormone epinephrine or adrenalin In 1897 Biedle demonstrated that the splanchnic fibers are secretory to the adrenal gland In 1908 Schur and Wiesel showed that when ether or chloroform is administered in anesthetic doses there is a marked increase in the secretion of adrenalin. Again, in 1912, Delbet, Herrenschmidt, and Beauvy asserted that the adrenalin content of the adrenal

medulla may be completely exhausted by chloroform anesthesia, and in the same year Elliot showed that ether, chloroform, and urethane, as well as hemorrhage itself, caused a marked increase in adrenalin secretion, even to the point of glandular exhaustion Since a denervated gland was not affected by anesthesia, it was concluded that the increased secretion of adrenalin was a result of the excitation of the sympathetic nervous system.

The fact of this sympathetic excitation has been frequently affirmed since 1921. Morphine, ether, chloroform, and urethane have all been specifically convicted. It has been shown (what every elementary student of physiology demonstrates for himself) that the so-called 'pressor' and 'depressor' reflexes are apparently fully active in the anesthetized animal. It has been shown that, during anesthesia, sensory stimulation induces not only reflex vasomotor action but also increased secretion of adrenalin. In ether anesthesia, at least, the sympathetic vasodilators may be excited simultaneously with the vasoconstrictors.

The technique of study of the renal circulation that was in vogue for many years consisted of a series of operations which might have been specially designed to excite autonomic nervous activity. First an anesthetic was administered, then the abdomen was incised and the viscera were exposed and pushed aside; blood vessels were dissected free and ligated, and sometimes the aorta and all its lower branches, other than the renal artery, were tied. The kidney was then forcibly freed of its attachments and manipulated in order to insert a stromuhr in the renal artery or vein, or the entire organ was thrust into an oncometer and put under some pressure. Every surgeon recognizes that laparotomy complicated by even slight visceral trauma presents a circulatory hazard, and circulatory inadequacy owing to decreased venous pressure and reduced cardiac filling is imminent in all anesthetized animals wherein the flaccid skeletal muscles and the open abdomen encourage the stagnation of blood Moreover, such animals are usually either overheated or overcooled and suffer progressive hemoconcentration and oligemia. There is little *a priori* doubt that venous pressure and cardiac filling are embarrassed in an anesthetized quadruped whose legs are forcibly extended while it is tied upon its back. If under these conditions vasoconstrictor activity does not approach a maximal level, it must indeed be because of the reign of chaos in the autonomic nervous system, or because the hardy and almost indomitable receptor systems of the aortic arch, carotid sinus, and other vasosensitive zones are either fatigued or depressed below the level of response When we add to this confusion the possibility that the anesthetic, which may be concentrated

in the tubular urine, may just as well disturb the responses of the tubules or the renal circulation as those of the cerebral cortex, it may be safely inferred that the anesthetized animal is no easy place for the physiologist to find his way about Surgeons have long been aware of the physiological disturbances associated with all forms of anesthesia; physiologists, less concerned with the ultimate fate of their subjects, have too frequently remained stubbornly oblivious to them.† [1979]

To return to Bernard's original observation, when the splanchnic nerves were sectioned in the anesthetized, laparotomized animal, the renal blood flow and the urine flow generally increased on the denervated side. Whether the explanation of 'denervated hyperemia' is simple or complex, it is not surprising that the phenomenon itself failed to be confirmed in the first observations to be made painlessly on the unanesthetized and untraumatized animal. Using the explanted kidney preparation, Rhoads, Van Slyke, Hiller, and Alving [1704] found that neither local anesthesia nor surgical denervation of the kidney had any effect upon the renal blood flow Lassen and Husfeldt [1216] observed no increase in the creatinine clearance in 4 normal subjects during spinal anesthesia; where the blood pressure fell, this clearance decreased but, when the pressure was maintained by ephetonin, the clearance remained practically unaffected. Smith, Rovenstine, Goldring, Chasis, and Ranges [1910] demonstrated in normal, unoperated subjects that spinal anesthesia, up to levels (T5 or higher) considerably above those at which the efferent sympathetic pathways to the kidneys emerge from the cord, does not produce renal hyperemia as judged by the diodrast clearance, nor does it have any other consistent effect upon the renal circulation. These investigators concluded that the renal blood flow is normally determined by autonomous, intrinsic activity of the renal arterioles and is not dependent upon tonic activity in the sympathetic pathways.*

* This conclusion was extended, on the basis of negligible blood pressure changes, to the arterioles of the body generally (exclusive of the skin) but specifically only in man in the resting, basal condition and in the supine position. [illegible]

tribute in some measure to the *vis a tergo* of venous return.

[illegible]

manipulation, such as laparotomy, and weight of abdominal retractors, hemostats, the pressure of packs and the pressure which assistants put upon the ab-

Complete surgical denervation of the kidney can be secured, according to Quinby,[1663] only by section and resuture of the artery, vein, and ureter.* Most investigators have been content, however, to divide all visible nerves entering the hilus or to cut the splanchnic nerves.

To return to the phenomenon of denervation diuresis, observations on unanesthetized animals lead to a result quite contrary to that which has been obtained over a period of 70 years in acute anesthetic experiments. In 1931 Bykow and Alexejew-Berkmann [312] explanted the ureters of a dog so that the urine flow of each kidney could be determined separately. One kidney was then denervated. After recovery from the operation, the urine flow remained almost identical on the two sides under all conditions. A similar technique involving explanted ureters was used repeatedly by Verney and his coworkers,[1135] who again found no difference in urine flow in the denervated as compared with the normal kidney. Subsequently Verney and his coworkers showed that the wide fluctuations in urine flow associated with water diuresis, with sensory stimulation, and with excitement and exercise are mediated in both the normal and denervated kidney in an entirely parallel manner by hormonal control, as shown in chapter x and figure 73. Grabfield and Swanson [832,833] and Hiatt,[904] utilizing exteriorized ureters in the unanesthetized dog, report that there are no significant differences in urine flow or renal blood flow between the normal and denervated kidney. Chasis and Michie [796] found that unilateral denervation in patients with essential hypertension does not increase the renal blood flow or the urine flow on the operated side. Although their observations were not designed to test the point specifically, no diuresis after denervation of a single remaining kidney was observed in the dog by Rhoads *et al*,[1704] or by Smith *et al.*[1940] and other investigators who have examined renal function in man during spinal anesthesia. The fact that water intake and urine output may be temporarily increased after bilateral denervation [941] may be referable to other factors and does not refute the many observations now avail-

dominal walls, as well as the manipulation of the viscera and hemorrhage itself, [illegible] and may

[illegible]

paralysis of the thoracicolumbar autonomic nervous system, the patient is deprived of nearly all defense against circulatory embarrassment. That such factors are chiefly involved is indicated by the absence of any severe circulatory changes during high spinal anesthesia in unoperated man'

* Professor Marshall relates that when Quinby wanted to denervate a dog's kidney he would remove it and pass it around among the spectators

able on unilateral denervation in the dog and man; and, in the nature of the problem, observations on anesthetized animals [1175] can no longer be considered pertinent to the question. Maluf [1176] transplanted a dog's kidney to the femoral region, exteriorizing the ureteral orifices. The reabsorption of water and chloride from the glomerular filtrate (inulin or creatinine clearance) remained identical in the transplanted (dener-

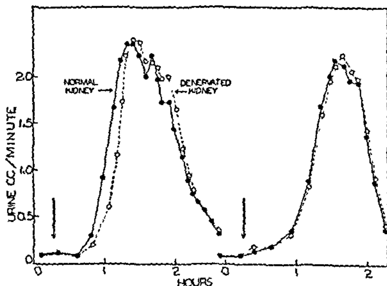


FIGURE 73. Diuretic response of the kidneys in the dog to water after section of the left splanchnic nerves. In the first test, 2 days after unilateral splanchnicectomy, 280 cc. of water were given by stomach tube; in the second test, 4 days later, 300 cc. were given. (Klisiecki, Pickford, Rothschild, and Verney [1139])

vated) and non-transplanted kidney, during both diuretic and antidiuretic conditions. The phenol red/inulin clearance ratio was also identical, indicating that transplantation had no effect on tubular excretion and no marked effect on blood flow. Moustgaard [1483] has also found that denervation does not affect the filtration rate or renal blood flow in dogs.

Like 'denervation hyperemia,' 'denervation diuresis' appears to be a release from enhanced vasoconstrictor tone engendered by anesthesia and traumatic operative procedures. The renal vasomotor pathways in man, and probably in other mammals, are normally at rest; like the sympathetic nervous system generally, they serve to meet the 'emer-

gencies' of anesthesia, hemorrhage, oligemia, traumatic excitation, fear, and shock so frequently created, among other ways, by unwary physiologists.

Despite the limitations of earlier methods, they sufficed to establish a number of important points about the renal circulation, to which we may add others that have been established subsequently.

The kidneys receive a rich supply of vasoconstrictor fibers via the thoracicolumbar sympathetics. The evidence is against the existence of vasomotor fibers of any kind in the vagus, and there *is no evidence of renal vasodilator fibers in the thoracicolumbar* sympathetic pathways.

Moderate doses of adrenalin and presumably mild sympathetic activity produce some degree of renal ischemia. Larger doses of adrenalin and strong sympathetic excitation produce a more marked ischemia and may render the kidney completely bloodless. No evidence exists that adrenalin in any dose produces hyperemia in the kidney (as it does in the skeletal muscle, the cardiac, pulmonary, and cerebral circulation, and in some visceral organs in some species) by vasodilation.

The renal circulation has a remarkable capacity to adjust itself *quickly in the face of changing arterial pressure* so that the renal blood flow tends to remain constant whether the arterial pressure rises or falls. This autonomy is not impaired by denervation, and *probably accounts in great measure for the constancy of the renal* blood flow during changes in blood pressure associated with spinal anesthesia in man. The renal circulation does not show reactive hyperemia (i.e. vasodilation after a period of ischemia).

Though many substances (caffeine, glucose, sodium chloride, sodium sulphate, salyrgan, histamine, theophylline, glycol, amyl nitrite, sucrose, phenol red, creatinine), when injected intravenously in relatively large quantities, have been reported to produce a momentary increase in renal blood flow, the hyperemic action of these agents is variable, fleeting, and probably nonspecific.

In unanesthetized and anesthetized dogs the kidney participates in the reflex vasoconstriction elicited by excitation of the sympathetic nervous system; the resulting renal ischemia is ac-

companied by a reduction in filtration rate and oliguria, the oliguria being in part attributable to the reduction in filtration rate, and in part to increased secretion of ADH.

Renal denervation in unanesthetized normal dogs and men does not produce renal hyperemia, the vasoconstrictor pathways being quiescent under basal conditions, nor does renal denervation have any significant effect upon the normal urine flow, upon water diuresis, or pituitary antidiuresis.

Unilateral nephrectomy increases the renal blood flow in the remaining kidney in both dog and man, the increase being of the order of 70 to 100 per cent and fully attained within a few weeks or months. This is accompanied by considerable hypertrophy of the remaining kidney.

There is no evidence that the renal nerves exert a trophic action on the kidneys There is no evidence of renal atrophy after renal denervation (observations in man extend over a period of 2 years or more).

The physiological control of the renal circulation remains almost a complete mystery. Future developments in this problem will doubtless come from isolated observations, such as are cited in the following pages, but the relative importance of these observations cannot be assessed at the present time.

CLEARANCE STUDIES ON RENAL BLOOD FLOW, ETC.

Oil of Juniper

Figure 74 has been selected as a 'control experiment' because it is, essentially, a negative one It concerns the action of a rather large dose (1 cc.) of oil of juniper in alcoholic emulsion on the renal circulation Many years ago, oil of juniper enjoyed a vogue as a diuretic, and this fact suggested that it might have some action on the filtration rate or renal plasma flow. The experiment serves chiefly to illustrate the method of examination. The subject was prepared for the measurement of renal clearances by the administration of water both the night before and early in the morning of the test in order to establish good urine flows. It is desirable to have the latter above 1 cc/min. if accurate urine collections are to be made Suitable plasma concentrations of diodrast

tion (fig. 78). Gaddum[730] believes that ephedrine acts only by potentiating the action of adrenalin, in which view, accepting the normal quiescence of the renal vasomotor pathways, it is not surprising that it is without renal action. In respect to cardiodynamic effects, ephedrine resembles adrenalin.[1675]

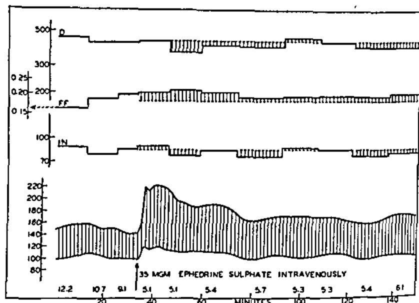


FIGURE 78. Action of ephedrine on renal plasma flow, etc, in a slightly hypertensive subject. (Smith[1881])

PAREDRINOL

Paredrinol, which appears to have a pure or predominantly vasoconstrictor action in man, mimics adrenalin in its renal action, reducing the renal plasma flow without a significant change in the rate of filtration. Cardiodynamically, it differs from adrenalin and ephedrine in that it consistently decreases cardiac output and increases peripheral resistance.[1676]

RENIN

Merrill, Williams, and Harrison[1442] found, in most of their experiments on anesthetized dogs, that single injections of renin increased the blood pressure and decreased renal blood flow; the kidney volume increased, as in the action of adrenalin. This paradoxical effect on renal blood flow and renal volume has been observed by others, who find that renin increases perfusion pressure through isolated kidneys[899]

Corcoran and Page[411 412] showed that the slow intravenous infusion of renin into unilaterally nephrectomized dogs with one explanted kidney caused a sustained reduction in the phenol red clearance, with variable effects upon the inulin clearances. Calculation of the renal plasma flow * from E_{PR} and E_{IN} showed that this decreased 35 per cent in the mean, the mean decrease in inulin clearance being only 13 per cent. This change in inulin clearance is less than is to be expected from the regression line relating spontaneous changes in renal plasma flow and inulin clearance, indicating that the filtration rate was generally somewhat increased relative to the existing plasma flow. But the 13 per cent decrease in filtration rate, opposed to an increase of 29 per cent in mean blood pressure, implies both afferent and efferent constriction, afferent predominating

E_{PR} averaged 0 485 ± 0 097 in the control periods and was not influenced significantly by renin or by the change in renal plasma flow. E_{IN} averaged 0.297 ± 0 077 in the control periods and was increased (+50 per cent) during renin infusion by the reduction in plasma flow, the clearance remaining nearly constant.

ANGIOTONIN (HYPERTENSIN)

It is generally accepted that angiotonin (or hypertensin) is the active pressor agent formed when renin-activator acts upon renin. Corcoran and Page[412] showed that, when infused into unilaterally nephrectomized dogs with one explanted kidney, angiotonin increased the arterial pressure, decreased the renal plasma flow, and increased C_{IN} The effects were similar to those observed during the infusion of renin but initially more profound and, after interruption of the infusion, more fleeting The filtration rate was generally decreased initially, indicating predominant action on the afferent arteriole, but after this transient effect the filtration rate tended to return to normal, indicating equal action on the afferent and efferent side

In man, the slow infusion of angiotonin reduces renal plasma flow without change in filtration rate, thus resembling adrenalin in its renal action. Unlike adrenalin [illegible]

Corcoran, Browning, and Page[408] have reported a subject with orthostatic hypotension who responded to a tilt of 60 degrees by syncope, hypotension, and decreased renal plasma flow. Angiotonin increased the

* The values of the mean flow separately calculated from E_{PR} and E_{IN} agreed within 1 per cent.

blood pressure and renal plasma flow. After treatment with the head-up bed, when the orthostatic hypotension had disappeared, angiotonin caused its characteristic renal vasoconstrictor effects. They accept the interpretation that, in orthostatic hypotension, the sensitivity of the arteriolar bed to normal vasoconstrictor influences is diminished

Pickering and Prinzmetal [1811] and Brandt and Grunn [245] have shown that renin injected intravenously in rabbits in doses greater than 1 unit produces a conspicuous diuresis of tubular origin, there being no increase in endogenous or exogenous creatinine clearance and generally a considerable decrease in PAH clearance. This diuresis is accompanied by a large increase in the excretion of protein, sodium, and chloride, the concentration of chloride in the urine tending to rise to or slightly above that of the plasma Smaller doses of renin have a slight antidiuretic effect.

Hypertensin acts similarly to renin in this respect; it increases urine flow and chloride excretion, the urine chloride concentration, whether high or low initially, approaching that of the plasma In the doses used, hypertensin and renin had no constant effect on the inulin clearances but always reduced the diodrast clearance. In the anesthetized rabbit, renin had no conspicuous effect on Tm$_D$ during the period of diuresis The evidence is compatible with the view that the changes in the volume and composition of the urine during diuresis produced by renin are mediated by hypertensin and are a result of reduction of the tubular reabsorption of water, sodium, and chloride.[1062] This action on the tubules has not been observed in the dog or man, and changes in the secretion of ADH are not excluded

Renin and angiotonin also produce in the rat transient proteinuria, which is attributed to increased glomerular capillary pressure.[16] This phenomenon is abolished by adrenalectomy and not restored by massive treatment with cortical extract or DCA [18]

ISUPREL

Isuprel [1-(3^1,4^1-dihydroxyphenyl)-2-isopropylaminoethanol hydrochloride] is a compound, related to adrenalin, which has a vasodepressor action It has been suggested that pharmacologically it resembles sympathin I, once assumed to be the naturally occurring vasodepressor substance related to adrenalin Corcoran and Page [426] find that isuprel produces a moderate increase in renal blood flow when injected intravenously in dogs, with no change in the filtration rate. The effect is augmented by the sympatholytic agent, tetraethylammonium, which also (paradoxically) augments the pressor and renal action of adrenalin.

PITRESSIN

Earlier investigators had reported a variety of results after the administration of pituitary extracts or of pitressin to anesthetized and unanesthetized animals, using a thermostromuhr to follow the renal blood

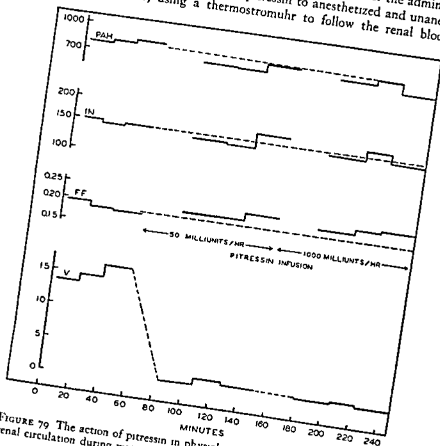


FIGURE 79 The action of pitressin in physiological doses on the urine flow and renal circulation during water diuresis in a normal subject

flow Many of the changes were very fleeting and earlier studies were complicated by the use of pharmacologic rather than physiologic doses. Corcoran and Page,[411] in observations on unilaterally nephrectomized dogs with one explanted kidney, found that the intravenous infusion of pitressin (8 to 100 milliunits/min.) caused an increase in renal plasma flow (+33 to +90 per cent), as calculated from E_{PR} and E_{IN}, in 5 out

of 11 experiments; in 6 experiments the changes were negative or slight. The inulin clearance increased in 5 experiments and showed negligible changes in the rest. E_{PR} increased in 2 and decreased (−28 to −45 per cent) in 4 experiments. The changes in renal function were so various that they do not reveal any characteristic hemodynamic pattern; the results are perhaps complicated by pitocin and by the dosage, which exceeds that required to maintain antidiuresis in the dog (5 milliunits/hr.) by 100 fold and more Retching, sometimes vomiting and defecation, usually occurred during the first half hour of the infusion, and hematemesis was observed once. From these disturbances, it may be concluded that the dosage was massive and it is of particular interest that, although there was a marked reduction in pulse rate, the pitressin had no effect on blood pressure, emphasizing the inadequacy of a pressor test in the standardization of the antidiuretic hormone.

Maxwell and Breed (pers. com.) have found that infusions in man of pitressin in physiologic doses (40 to 100 milliunits/hr.) and in larger doses (1000 to 5000 milliunits/hr.) have no significant effect on renal plasma flow or filtration rate (fig. 79). In 16 subjects there was a consistent slight downward trend in C_{PAH} during the administration of pitressin; C_{PAH} declined in 13 subjects and increased in 3. This fall was never marked, however, and averaged less than 7 per cent of control levels. The inulin clearance, E_{PAH}, and renal arterial-venous oxygen difference did not change significantly.

ATROPINE

Corcoran and Page[411] report that, during the infusion of pitressin, atropine (0 065 mg. intravenously) had no consistent effect on renal plasma flow, E_{PR}, or phenol red clearance in unilaterally nephrectomized dogs with one explanted kidney. E_{IN} and the inulin clearance increased, the latter by 9 to 23 per cent, in 5 of 7 experiments. Blood pressure increased by an average of 40 per cent over the level existing during the administration of pitressin. The experiments again emphasize the independence of the renal blood flow and systemic arterial pressure, and the absence of parasympathetic cholinergic innervation in the renal circulation.

ORTHOSTATIC HYPOTENSION

When a person assumes the upright posture, the blood tends to accumulate in the subcardial regions, particularly in the capillary and venous channels, and fluid leaves the vascular tree for the

interstitial space, causing some hemoconcentration. He normally resists venous failure by walking to and fro or shifting his weight from one foot to the other, the contractions of the leg muscles, aided by the venous valves, promoting the return of blood to the right heart If, however, he stands still, as in leaning motionless against a wall, or if he is tilted to 60 or 70 degrees on a tilt-table,

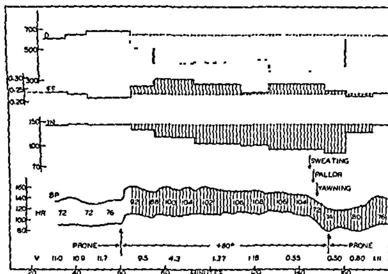


FIGURE 80 Renal ischemia induced by tilting a normal subject on a tilt-table (Smith [1925])

progressive venous stagnation leads to decreased cardiac output and vasoconstriction until the cerebral circulation is inadequate and syncope occurs. Through the sino-aortic receptors, the first lowering of mean arterial pressure elicits vasoconstriction throughout the body.

Figure 80 shows the course of events in a subject who, after 3 control periods in the recumbent position, was tilted head up to 80 degrees, remaining in this position until he fainted. As soon as he assumed the orthostatic position, the renal plasma flow decreased; in view of the fact that the mean arterial pressure did not decrease but was in fact slightly increased, this renal ischemia

must be attributed to externally imposed constriction of the renal arterioles. All subjects do not respond alike to this ordeal, but qualitatively the renal effect is invariably vasoconstriction.[1929, 1931]

It will be observed that, in the subject illustrated in figure 80, syncope was accompanied by an abrupt slowing of the heart. Bradycardia or cardiac arrest is stated to be the second most common mechanism involved in fainting, the most common being abrupt vasodilatation following enhanced vasoconstrictor activity.[607]

The hepatic blood flow is also reduced during a period of quiet standing.[232]

Where the upright position is maintained for a shorter time, the changes in renal circulation are less marked but qualitatively similar to those described above.[2209] Brun, Knudsen, and Raaschou [234] have shown that oliguria persists after orthostatic syncope, despite rapid restoration of the filtration rate; they attribute the oliguria to secretion of ADH.

Deyrup [509] has shown that the filtration rate, which remains unchanged for a period of 2.5 hr. in dogs in the supine position, decreases slowly by 20 to 50 per cent when the animals are kept standing

Ni and Rehberg [1520] observed a marked drop in the exogenous creatinine clearance in the orthostatic position, and they obtained a fair inverse correlation between the creatinine clearance and the colloid osmotic pressure of the plasma, leading them to suggest that the increase in the latter was responsible for the decrease in the filtration rate. This causal relationship is, however, open to question since vasomotor changes in the kidney seem to dominate the changes in renal function. Hemoconcentration simply parallels circulatory inadequacy.

It has been reported by several investigators [1929] that in the dog the renal vascular bed does not participate in the vasomotor reflexes concerned with the maintenance of arterial pressure and mediated through the sino-aortic receptors, but the negative reports are based on anesthetized-laparotomized animals Handovsky and Samaan [905] claim that this is not true in the postoperative, unanesthetized animal, and Malméjac and Donnet [1375] report renal ischemia after section of the sino-aortic nerves in chlorolosed dogs Similarly the data of Bing, Thomas, and Waples [173] demonstrate renal vasoconstriction in dogs with sino-aortic denervation. There may be a difference between the response in dog and man because of the quadrupedal and bipedal habitus, but as the evidence stands it appears that in both species the same cardiovas-

cular stimuli evoke comparable renal vasoconstriction. The decrease in the filtration rate in the face of maintained arterial pressure indicates marked afferent constriction.

Gabriele[729] has examined the effects of changing the piezometric angle of the renal artery in anesthetized (nembutal) dogs. When the kidney was moved cephalad and the aortic-renal artery angle reduced to 45°, the mean blood pressure and pulse pressure in the renal artery were reduced and the renal plasma flow decreased by about 36 per cent. The author suggests that a naturally high piezometric angle may be related to 'a predisposition toward hypertension,' and that elevation of the kidney during pregnancy may be related to toxemia of pregnancy, but the total evidence indicates that the renal circulation has nothing to do with the causation of either disease. Movement of one or both kidneys may, however, be related to changes in renal function in the upright position as compared with the recumbent position, though the available data show changes qualitatively opposite to those to be expected from this cause alone.

INCREASED ARTERIAL PRESSURE

Acutely raised intracranial pressure in anesthetized (barbital) dogs in which osmotic diuresis is maintained with glucose or sucrose causes a marked decrease in urine flow despite the accompanying great rise in systemic blood pressure. In dogs in which one kidney is denervated, diminution of urine flow occurs in the normal kidney, whereas diuresis is maintained or increased in the denervated kidney. The reduction of urine flow in the normally innervated kidney is probably due to renal vasoconstriction resulting from asphyxial stimulation of the vasomotor center.[1763]

NEUROGENIC HYPERTENSION

After section of the buffer nerves the renal blood flow in the unanesthetized dog either remains constant or decreases slightly, despite a marked increase in arterial pressure. The overall renal resistance is increased by 20 to 80 per cent, whereas the peripheral resistance shows a much smaller change. To what extent this represents autonomous adjustment within the renal circulation cannot as yet be determined.[173]

Acute elevation of the blood pressure by 43 per cent, induced by clamping the carotid arteries in unanesthetized rabbits in which the kidneys are denervated and the adrenal glands demedullated, is accompanied by an average increase in filtration rate of only 8 per cent and in renal plasma flow of 5 per cent. In some instances the renal plasma flow decreased during hypertension. Renal autonomy is preserved without me-

diation of neural reflex action or secretory activity of the adrenal medulla in this species,[680] as in the dog[1929] and man.

FRIGHT

In the emergency theory of the function of the sympathetic nervous system, so well developed by Cannon, fright is placed high in the list of effective stimuli, exceeding even hemorrhage

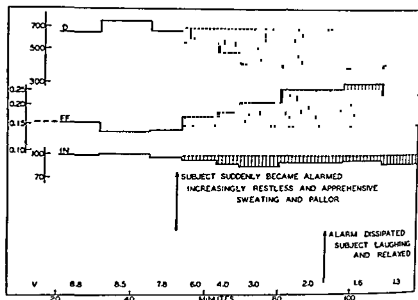


FIGURE 81. Psychogenic renal vasoconstriction during alarm. (Smith[1974])

and anger in its potency. During the series of clearance determinations illustrated in figure 81, the subject suddenly became alarmed through misunderstanding about the significance of the clearance procedure. He became increasingly restless, apprehensive, and remonstrative, and sweating and pallor indicated marked sympathetic excitation. He was so perturbed that it was impossible to make blood pressure measurements, but one can be confident that the mean blood pressure did not fall. When, after 40 min., his alarm was abruptly dispelled, his apprehension was replaced by relaxation, laughter, and the best of humor. The renal vasoconstriction that occurred at the peak of his alarm was as profound as that which is seen after the administration of large doses of

adrenalin and indeed persisted through the last observation The response is typical of adrenalin and it is, of course, impossible to exclude the action of this hormone, but in view of their well-established function it would be equally arbitrary to exclude the participation of the renal vasoconstrictor nerves. (A second study of this type is illustrated elsewhere.[1929])

PAIN

Using a headpiece with adjustable thumbscrews to elicit controlled and reproducible pain in man, Wolf [2242] has shown that pain which is tolerable for considerable periods induces a marked decrease in both renal plasma flow and filtration rate. The plasma flow was sometimes reduced to less than one-third of the control, the filtration rate to one-half. Having the subject immerse a hand in cold water to the limit of endurance was less effective, though the clearances decreased in 2 out of 3 instances after the hand was removed The reduction in the filtration rate indicates dominant afferent action, as in the case of orthostatic syncope.*

PSYCHONEUROTIC CONFLICT

A decrease of 20 per cent or more in renal plasma flow may occur in subjects with early essential hypertension when the discussion turns to

* Continuing a quotation started on p 414

'We do not suppose that every alarm and apprehension has its concomitant of increased renal vasoconstrictor tone the autonomic nervous system is too complex for easy generalization I present these observations chiefly that I may return to an earlier point if emotional disturbance, even of an extreme nature, can so markedly influence the renal circulation in man, what must we say of procedures in laboratory animals which entail profound and almost maximal sympathetic excitation by alarm and fright, by the administration of anesthetic, by excitation of sensory nerves, by surgical incisions, by the handling of the viscera, by circulatory inadequacy, by the manipulation of the kidney itself I would enter no special plea for the uncontrolled use of the clearance method in renal physiology until it has been more rigorously tested, and other methods are greatly needed to reinforce and supplement it. What I would plead is that the history of renal physiology has been in too large measure a history of traumatic procedures which have in the end only misled investigation, and that far more is to be gained by spending several years in perfecting a non-traumatic, truly physiological method than one year in applying a traumatic one Perhaps it is not too much to suggest that, so far as *immediate* experimental procedures are concerned, any observation that is too traumatic to be safely, reasonably and ethically carried out upon man is too traumatic, as far as physiological validity is concerned, to be carried out upon an experimental animal.' [1929]

topics of traumatic significance in the life situation. The filtration rate remains unchanged. An increase in *renal plasma flow occurred in one* subject when feelings of security were induced with the aid of sodium amytal. A change in renal hemodynamics is not invariable under such circumstances, however. Under presumably similar excitation, the renal response is abolished by sympathectomy.[2263] The significance of this response, so far as the genesis of *essential hypertension is concerned, is in* doubt, however, because significant changes, both positive and negative, were obtained by unpleasant psychiatric interviews in 4 out of 11 experiments on 7 young males, 5 out of 8 experiments on 8 older males, and 4 out of 8 experiments on 6 females, all of whom were normotensive.[336]

COLD PRESSOR TEST

Talso, Crosley, and Clarke[2044] report that, when normal subjects immersed one foot in ice water at 1° C. for 15 min., the filtration rate and renal plasma flow were decreased by 14 to 21 per cent, respectively, this *decrease occurring either during the application of the cold stimulus or* within some 30 min. thereafter. The decrease in urea clearance, chloride excretion, and urine flow reported by others[1541] may be related to this decrease in filtration rate. The decrease in urine flow is not abolished by inhalation anesthesia and may involve an increased secretion of *ADH elicited by pain.*[1542] *White and Rolf*[2209] *report one* experiment in which one hand and about a third of the forearm were immersed in ice water at 0° C until the pain became intense; the hand was then withdrawn for a minute and the cycle repeated. Only slight reduction in clearances was observed, and no change occurred when the hand was *immersed in water at 15° C.*

HISTAMINE

Histamine reduces both the creatinine and urea clearances, but there is a simultaneous reduction in mean arterial pressure, and consequently the *renal effects are difficult to interpret.*[177] *In normotensive* and hypertensive subjects, histamine in subcutaneous doses sufficient to evoke a moderate general reaction caused slight reduction in the renal plasma *flow, with no significant changes in the filtration rate,* the filtration fraction increasing.[1698]

EXERCISE

Covian and Rehberg[441] showed that exercise in man has an antidiuretic effect and, if the exercise is severe, it is accompanied by a decrease in the urea and creatinine clearances and sometimes by albuminuria.

Barclay, Cooke, Kenney, and Nutt [62] examined the effects of a one-quarter mile run at full speed in 10 normal subjects. On the average, exercise reduced the renal plasma flow to 70 per cent and the filtration rate to 55.4 per cent of the control values (single injection method). The filtration fraction fell from an average value of 0.158 to 0 126. All subjects were in a state of water diuresis Exercise appears to annul the antidiuretic action of pitressin, relatively more water being returned and the duration of diuresis being prolonged.[85]

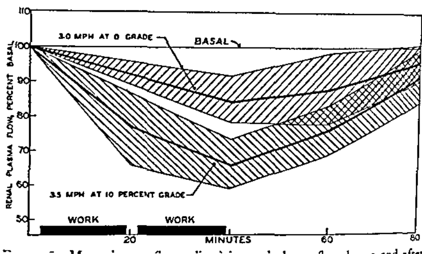
Merrill and Cargill [1440] examined the effects of stepping up and down 2 steps, each 12 5 in high, approximately 40 times, or of exercising the legs by means of a two-pedal pulley and weight device. The exercise appears to have been moderately taxing to the individual. In most cases exercise was accompanied by moderate to marked reduction in renal plasma flow and filtration rate, but in none did the filtration rate fall as low as 70 cc/min , the value that the authors consider critical for the excessive retention of sodium The authors conclude that the renal blood flow is reduced when the circulation is overtaxed by moderate exercise, a phenomenon that would be exaggerated in cardiac disease.

White and Rolf [2203] (single-injection method) examined the effects of running exercise While light exercise led to only slight reduction in renal plasma flow and filtration rate, moderate to severe exercise reduced these values to half or less of the resting levels and at least doubled renal vascular resistance, while brief maximum exercise reduced them to 20 per cent or less and increased renal resistance at least fivefold A longer period of maximal exercise at a lower rate was less effective, reducing clearances to about one-third of the resting values. The more intense the exercise, the greater the effect, and under extreme conditions White and Rolf predict that almost a liter of blood per min. may be made available for the circulation of active regions Recovery of clearances may be incomplete 60 min after cessation of exercise.

Protein did not appear in the urine formed during even the severest exercise, but, after severe exercise, was present in the first one or two postexercise samples The authors interpret this fact as indicating that exercise induces generalized vasoconstriction and that only at maximal work levels do any large number of glomeruli drop out of function and suffer ischemia to the extent that they begin to leak protein.

Reductions in renal plasma flow during short periods of exercise are reported by Aas and Blegen [2] Kattus, Sinclair-Smith, Genest, and Newman [1093] report that standing quietly but not motionless and walking on a treadmill at 3 m p.h have no effect on the filtration rate and only a moderate or no antidiuretic effect

Radigan and Robinson[1667] have compared the effects of exercise (3 m.p.h. up a 5 per cent grade on a treadmill) in cool (21° C.) and hot (50° C.) environments. In the cool environment, the resting filtration rate averaged 108 cc., and exercise did not influence it. The resting renal plasma flow averaged 695 cc., and exercise decreased it by 42 per cent. In the hot environment, the resting filtration rate was 84 cc. and exercise decreased it to 70 cc. The resting renal plasma flow in the hot en-



Keys[352])

vironment was 426 cc., and this decreased by 36 per cent during exercise

Exercise superimposed on water or alcohol diuresis decreases the pH and increases the excretion of titratable acid and of ammonia.[580] The renal ischemia associated with exercise in man is not hemodynamically typical of the action of adrenalin.[80]

Exercise also reduces the hepatic blood flow.[232]

Chapman, Henschel, Minckler, Forsgren, and Keys[352] examined men exercising on a motor-driven treadmill at energy outputs corresponding to 419, 612, and 1070 cc. of oxygen per min. per sq. m. The highest level sufficed to tax normal active males only moderately, but caused considerable discomfort in subjects accustomed to little or no strenuous exertion. During the first 16 min of exercise, the renal plasma flow decreased by an average of 6, 17, and 25 per cent of the resting control value at the three rates of exercise. Continued walking for another 16 min. yielded average reductions of 15, 27, and 37 per cent of the resting

control values. The renal plasma flow had not returned to basal levels after 40 min of recovery (fig 82). The authors note that, at the lightest rate of exercise, about 150 cc/min. of blood are diverted from the kidney for circulation elsewhere For the heaviest work load, the corresponding figure is about 330 cc, a not inconsiderable amount. Similarly, Chapman, Henschel, and Forsgren [351] found that during moderate exercise of relatively long duration the renal plasma flow decreased in 4 young men by 9 to 23 per cent, during the second 16 min period it decreased by 15 to 37 per cent and during the third 16 min. period by 19 to 34 per cent During the second and third hours of exercise, there was little further change In 2 men examined, the renal plasma flow had returned to within 10 per cent of the control value 1 hr. after cessation of exercise

HYPOXIA AND SIMULATED ALTITUDE

Most investigators report that anoxic hypoxia in unanesthetized animals and man causes transiently a moderate to marked diuresis with generally increased chloride excretion [60, 1212, 1447, 1891, 2030, 2031] In anesthetized animals, on the contrary, anoxic hypoxia usually leads to oliguria or anuria [1374, 1794, 1892, 2030, 2031, 2082, 2090] Stickney, Northup, and Van Liere [2099] conclude that mild hypoxia in anesthetized dogs generally produces polyuria, while severe hypoxia produces oliguria, but the incidence of either appears to be affected by the type of anesthetic agent used Since hypoxia may affect the tubular epithelium, the renal circulation, the secretion of adrenalin and antidiuretic hormone, and possibly the secretions of the adrenal cortex, these changes in urine flow as well as changes in the composition of the urine are uninterpretable without further information

McCance [1288] reports a subject who suffered syncope from apnoic anoxemia following voluntary ventilation During the ensuing oliguria, the rate of excretion of creatinine and sulphate were reduced to three-quarters and two-thirds, respectively, of their initial values, indicating a marked reduction in the filtration rate Urea excretion was reduced even more, probably because of the oliguria Ammonia formation and the capacity to form a concentrated urine were not affected

Caldwell, Rolf, and White [321] repeatedly subjected an army pilot and an untrained subject to 9.3 to 13.0 per cent oxygen for periods up to 19 min., with no effects on filtration rate, renal plasma flow, renal vascular resistance, or plasma glucose levels

Exposure of 5 normal male adults to simulated altitudes of 10,000 to 18,000 feet for 4 to 6 hr daily, 6 days a week, caused no change in renal plasma flow, filtration rate, or urine flow over periods of 4 to 6 weeks

Tmd, however, increased within 3 weeks at altitude, and this increase persisted for weeks or months after discontinuance of exposure The increase ranged from 10 to 35 per cent. The intermittent exposure to low oxygen tensions had no immediate detrimental effect on the kidney.

Acute exposure of dogs to simulated altitudes of 18,000 and 24,000 feet had no consistent effects on the filtration rate. In observations starting 5 min. after reaching altitude, the renal plasma flow increased in all dogs at 18,000, and was further increased in 1 dog at 24,000 feet, but decreased below the ground level values in the others. In 7 observations, TmPAH was unchanged, but in 3 observations this value increased by 88, 135, and 222 per cent [1314] TmG was significantly decreased in 2 of 3 animals at 18,000 feet [1107]

Reduction of the arterial oxygen tension to 50 mm Hg in 9 subjects, 7 of whom were normal and 2 emphysematous, produced only slight changes in filtration rate (−5.2 to +22 8, average +6 per cent) or renal plasma flow (−1.3 to +29 4, average +13 per cent).

The most pronounced effect was on the excretion of sodium, which increased from 162 to 256 μmEq/min , and chloride, which increased from 161 to 245 μmEq/min. The effects on urine flow, pH, and the excretion of potassium, phosphorus, and ammonia were negligible. The authors note that anoxic hypoxia probably does not contribute to the reduction in renal plasma flow or the retention of sodium and water observed in congestive heart failure.[125]

Aas and Blegen [2] observed a slight increase in renal plasma flow in 2 normal subjects breathing 9 5 per cent oxygen, the filtration rate decreasing slightly. Equivocal results were obtained in 2 patients in congestive heart failure

Renal vasoconstriction, as judged by paling, occurs in anesthetized (nembutal) laparotomized rabbits when the trachea is occluded, the renal blood flow being restored when air is allowed to enter the lungs These vasomotor effects are reduced or prevented by renal denervation.[633]

PRESSURE RESPIRATION

When respiration is carried out for 30 min. periods against pressures of 10 to 40 mm Hg above ambient pressure, the urea clearance and urine volume undergo progressive reduction, apparently reflecting a reduction in filtration rate [546]

ABDOMINAL COMPRESSION

Bradley and Bradley [235] studied the effects on the renal circulation of increasing the intra-abdominal pressure by the application of a pneu-

matic abdominal pressure girdle Measurements of the venous pressure in the inferior vena cava and renal vein by venous catheterization revealed that a compressional pressure of 80 mm Hg raised intra-abdominal venous pressure to about 20 mm. Hg, as compared to 2.9 to 7.4 mm Hg normally. The PAH clearance and filtration rate were invariably reduced by increased intra-abdominal pressure, on the average by −24.4 and −27.5 per cent, respectively The filtration fraction showed no change The authors believed that the elevation of renal venous pressure was probably sufficient to account for the reduction in renal plasma flow, but in view of other studies on renal venous pressure this remains doubtful. E_{PAH} was not changed during compression, showing that there was no arteriovenous shunting

Tm_D was reduced significantly by compression in 5 subjects, in about the same proportion as the filtration rate and renal plasma flow, so that the ratios C_{IN}/Tm_D and C_D/Tm_D remained about constant Tm_G fell in 3 out of 5 subjects studied, also in proportion to the filtration rate, so that the ratio C_{IN}/Tm_G also remained constant. The authors believe, since the diodrast clearance, the inulin clearance, Tm_D, and Tm_G were equally reduced, that the rise in venous pressure is accompanied by a rise in pressure in the renal pelvis, which blocks urine outflow from those (longest) nephrons in which the terminal pressures are lowest. As a result, all excretion in these nephrons ceases and all functions (C_{IN}, C_D, Tm_D, and Tm_G) are decreased proportionally Renal hyperemia did not occur after release from compressional ischemia

It is noteworthy that compressional ischemia was accompanied by an increased reabsorption of water, even in one subject with diabetes insipidus, implying that some change in renal hemodynamics is modifying tubular activity This matter is further discussed in chapter XXII.

French, Moland, and Booker [498] report that in dogs an increase to 10 mm Hg or less in intra-abdominal pressure has no effect on the filtration rate At pressures of 20 to 30 mm this function is decreased, and it falls to low levels at 40 to 50 mm The phenol red and creatinine clearances tend to return to normal in chronic experiments if the pressure is not increased too rapidly, indicating compensation, but remain reduced at the higher pressures

HOT ENVIRONMENTAL TEMPERATURE

Byfield, Telser, and Keeton [309] examined the effects of environment, as between a comfortable atmosphere (83 5° F, 2 per cent humidity), a hot dry atmosphere (99 5° F, 19 per cent humidity), and a hot wet atmosphere (99 5° F, 55 per cent humidity) on peripheral blood flow and

renal function. The higher temperature increased peripheral blood flow about fourfold but was without effect upon the filtration rate in 20 subjects. Two normal subjects and 3 with essential hypertension (in all of whom the filtration rate was above 110 cc.) showed only small changes in the renal plasma flow in the hot room; but in 2 subjects with essential hypertension and 1 with chronic glomerulonephritis, in whom the diodrast clearance was reduced (129 to 580 cc.), this clearance dropped by *16 to 42 per cent. Two other nephritic subjects with low diodrast clearances* (76 and 119) showed no change. It appears that hot environmental conditions do not increase renal plasma flow and, if shunting of blood to the periphery is marked, may substantially decrease it. The marked decrease in both filtration rate and renal plasma flow in a hot environment reported by Radigan and Robinson [1667] has been discussed under exercise. In 6 trials, 4 subjects showed no change in Tm_D, but in 1 normal and 1 hypertensive subject this function increased by 48 and 33 per cent, *respectively This observation recalls the abrupt increases in* Tm_D recorded above in decompression and, on confirmation, would be *of considerable interest relative to tubular metabolism.*

DIATHERMY AND FEVER

Conventional diathermy was reported by Grant and Medes [846] to increase the filtration rate in dogs, but Nicholes, Boynton, and Herrin [1521] obtained only slight increases by this method, and Page [1564] observed no significant change in the urea clearance during fever therapy in normal subjects or patients with renal disease. Farr and Moen [626] observed only negligible changes in the urea clearance of rheumatic fever patients heated by carbon filament lamps. When hyperthermia was induced in dogs by electromagnetic induction, *the filtration rate decreased by* 12 to 79 per cent. Section of the splanchnic nerves and removal of the lumbar sympathetic ganglia nearly or completely abolished this decrease [1521]

Electromagnetic induction of heat in the region of the kidney also caused a slight decrease in the urea and creatinine clearances in patients with essential hypertension, acute rheumatic fever, and renal disease.[190]

ANESTHESIA

Pentobarbital sodium anesthesia (30 mg/kg. intraperitoneally) produced no consistent change in the inulin and diodrast clearances or in Tm_D in dogs.[418] *This anesthetic does not depress the diodrast extraction ratio,*[419, 429] from which it may be concluded that the renal plasma flow is not changed during anesthesia (from 129 ± 4.8 to 146.7 ± 21.1 mm. Hg); and the unchanged diodrast clearance and filtration fraction im-

ply autonomous renal vasoconstriction in the face of elevated blood pressure.

In 3 of 37 dogs, renal failure occurred during anesthesia; the diodrast and inulin clearances were extremely low and in 1 instance were observed to fall abruptly with only a slight increase in filtration fraction (0.23 to 0.27), while the mean arterial pressure was maintained at 116 mm. Hg or above The cause of renal failure was undetermined, but the authors suggest renal arteriolar constriction, since others have observed that thiobarbiturate given intravenously may increase blood pressure and simultaneously decrease kidney volume.

Repeated anesthetization of dogs with cyclopropane, ether, and chloroform over a period of 8 months does not affect the maximal urea clearance Ninety-one control determinations on 5 animals averaged 34.9 ± 6.1 cc (σ/m = 0.176), and 83 determinations after 19 periods of anesthesia with the 3 agents averaged 35.2 ± 5.9 (σ/m = 0.166) cc/min. per sq. m [1667]

Craig, Visscher, and Houck [447] have shown that light ether and cyclopropane anesthesia (stage III, plane 1) in dogs produces no significant alteration in PAH or creatinine clearances, but in deep anesthesia (stage III, plane 3), uncomplicated by surgical operation, depression of renal function occurs; the PAH and creatinine clearances were reduced to 53 ± 8.9 and 48 ± 7.7 per cent of the values observed during light anesthesia, *despite maintenance of arterial pressure. The filtration fraction* fell only very slightly (to 91 ± 3.2 per cent) These clearances returned substantially to normal when the animal was allowed to recover from stage III, plane 3, to stage III, plane 1 The reduction in creatinine and PAH clearances in deep anesthesia were attributed to neurogenic constriction of the afferent arterioles Reduction in glucose Tm at load/T_G ratios above 1.25 indicates that glomerular activity was reduced much more in some nephrons than in others Repeated anesthesia did not alter glucose Tm when measured without anesthesia. Deep anesthesia decreased urine flow to 41 ± 3.6 per cent of the value observed in stage III, plane 1 The decrease in filtration rate could well account for this oliguria, especially since mannitol or glucose was infused to maintain osmotic diuresis, but increased secretion of antidiuretic hormone cannot be excluded

Coller, Rees, Campbell, Iob, and Moyer [398] state that inulin and diodrast clearances in man are not affected by ether anesthesia, provided the anesthesia is well controlled and significant blood volume reduction does not occur Inulin clearances in 4 patients studied under cyclopropane anesthesia were depressed; in 2 patients the diodrast clearance in-

creased and in 2 it decreased. Ether and cyclopropane appear to have no effect on ammonia production.

Burnett, Bloomberg, Shortz, Compton, and Beecher[298] *report that* in 8 patients during ether anesthesia maintained in stage III, plane 2, the mannitol clearance was reduced by an average of 21, the PAH clearance by 39, and the urine flow by 51 per cent. The filtration fraction was increased by an average of 25 per cent. In 7 patients receiving cyclopropane, these changes were −31, −52, −47, and +35 per cent. While qualitatively the effects of ether and cyclopropane on renal function are similar, quantitatively cyclopropane was believed to be more active in reducing renal function.

The administration of ether to rabbits invariably reduced the filtration rate, renal plasma flow, glucose Tm, and urine flow, without significant changes in systemic blood pressure. These effects were transient and passed off during anesthesia, indicating that they are neurogenic responses to the administration of an irritant anesthetic agent. The rabbit is apparently more sensitive in this respect than the dog or man However, the intravenous administration of sodium pentobarbital can produce deep anesthesia in the rabbit without disturbance of renal function.[678]

If the decreased urine flow and clearances associated with deep anesthesia are attributable to neurogenic vasoconstriction, as Craig *et al.* point out, an explanation is provided for the diuresis and renal hyperemia, which, in the older literature, were attributed to renal denervation In the 30 studies cited by Smith,[1929] beginning with those of Claude Bernard in 1859, the anesthesia must have been fairly deep, probably deep enough to depress the renal blood flow and filtration rate *Under* these conditions, denervation might be expected to block vasomotor activity and to permit the renal blood flow and filtration rate to increase

In addition to the studies on spinal anesthesia discussed in the early part of this chapter, other studies on subjects with essential hypertension are cited in chapter XXIII.

RENAL VASODILATATION

Pyrexial Hyperemia

Attention has been called to the fact that inulin—as indeed almost any organic or inorganic material—may become contaminated by bacteria, molds or yeast, the proteins of which, on parenteral administration, prove pyrogenic, i.e. they induce chills,

fever, headache, nausea, lumbar and other pains in the familiar manner of typhoid vaccine. The reaction is most severe when pyrogenic material is given intravenously. Early in investigations utilizing inulin, it was found that this substance may be contaminated with pyrogen to the extent that, where 150 gm. of nonpyrogenic inulin could be given intravenously to man without

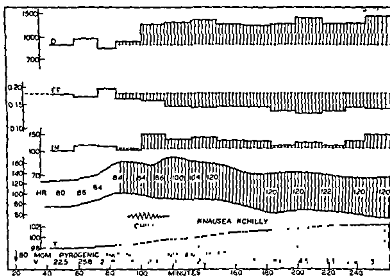


FIGURE 83. Renal hyperemia induced by pyrogen in a normal subject with no premedication. Note the chills, nausea, increase in blood pressure and heart rate, and the rise in rectal temperature, T

This test was made 1 week after the observation in figure 84 in order to circumvent the possibility that the reaction might be diminished by antibody formation. (Smith [1929])

any disturbance whatever, 50 to 150 mg. of pyrogenic (*toxic*) inulin would produce a severe pyrexial reaction. It was also an early discovery that among the sequelae of this reaction is a remarkable increase in renal blood flow. Triple typhoid vaccine and other pyrogens have this same action, and both pyrogenic inulin and triple typhoid vaccine have been used to produce sustained renal hyperemia in animals and man, this being an effective method of attaining this end.[237, 256, 258, 798, 993, 1929]

Figure 83 shows the effects of 80 mg. of pyrogenic inulin ad-

ministered intravenously to a normal subject without premedication. Characteristically, a latent period of 70 to 90 min. intervenes after the injection of the pyrogen before any physiological disturbance is evident; this latent period extends over the first 3 urine collection periods in figure 83, and these may be taken as control values. Typically, about an hour after injection the blood pressure begins to rise, and the subject complains of chilliness (peripheral vasoconstriction). Soon a more or less severe chill occurs, and with the chill the body temperature begins to rise and continues to rise for 3 to 4 hr. regardless of whether there are more chills or not. At the peak of the reaction there may be additional chills, nausea, headache, back pain, and other symptoms of febrile reaction. At about the time of the chill, the renal plasma flow begins to increase; this increase is frequently but not invariably preceded by a short phase of renal ischemia. Renal hyperemia usually persists for 4 hr. or more. In general, the hyperemia will range from 30 to 60 per cent above the control value, though increases of 100 per cent have been observed—the relative increase, of course, depends in great measure upon the control level. It is perhaps more exact to say that at the peak of hyperemia the renal whole blood flow will reach 2000 to 2500 cc/min., the largest figure on record being 3000 cc. (The average normal figure in men is 1166 cc/min.) The fact that the increase in blood flow is accompanied by a reciprocal change in filtration fraction (the filtration rate remaining constant) shows that both afferent and efferent arterioles are dilated. (Other studies on pyrexial hyperemia are illustrated elsewhere.[237, 1931])

This phenomenon of renal hyperemia is naturally of great interest and an early effort was made to control the fever and other adverse reactions by various means. It was found that the administration of a suitable dose of the antipyretic, aminopyrine, produces in this complex response a remarkable dissociation. Figure 84 shows observations on the same subject as in figure 83, after the same dose of pyrogen but now *premedicated* with aminopyrine (10 grains every 4 hr. during the preceding 16 hr.). This experiment was carried out before the one shown in figure 83, in order to circumvent the possible development of tolerance to the pyrogen. Under aminopyridine medication, the rise in blood pres-

sure, the chill, the nausea, all aches and pains, as well as the rise in body temperature, are abolished; one would not know that the subject had received pyrogen, yet the renal hyperemia still appears and, as far as can be judged, is not diminished either in magnitude or duration.

Pyrexial hyperemia is not dependent upon the renal nerves;

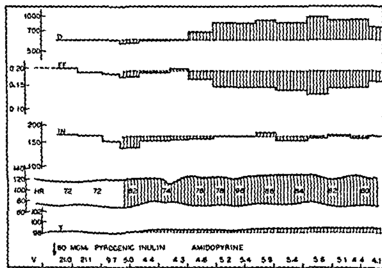


FIGURE 84 Renal hyperemia induced by pyrogen in the same subject as is shown in figure 83, but after premedication with amidopyrine (10 grams every 4 hr. during the preceding 18 hr.) Note the absence of all febrile disturbances, despite the persistence of the renal hyperemia (Smith [1951])

Goldring *et al.*[793] found that a fair degree of hyperemia was induced by pyrogen in 3 sympathectomized hypertensive subjects, in one of whom the kidneys were examined separately before and after unilateral sympathectomy, while Hiatt [893] has shown that pyrexial hyperemia in the dog is essentially unmodified by renal denervation (fig 85). It appears, therefore, that the dilatation of the renal arterioles is effected either by a local action of the pyrogen (or some derivative) on these arterioles or by the secretion, perhaps elsewhere in the body, of a vasodilatory agent which is transmitted to the kidneys by the blood. The first is the more likely interpretation.

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pertension [798] and to observe the effects of the repeated induction of renal hyperemia on blood pressure in hypertensive subjects.[316]

Maxwell, Morales, and Crowder (pers. com.) have shown that E_{PAH} is not reduced during hyperemia.

The hepatic blood flow is also increased during the pyrexial reaction, *in one subject from 2 to 4.0 liters/min.*,[232] *hypatic hyperemia*, like renal hyperemia, being uninfluenced by premedication with aminopyrine [233]

ADENYLIC ACID, ADENOSINE, AND ADENOSINE TRIPHOSPHATE

Adenylic acid derivatives are known to be powerful vasodilators and, since they are natural tissue metabolites, their action on the kidneys is of some interest Houck, Bing, Craig, and Visscher [1041] have examined the effects of the continuous intravenous infusion of yeast (3-adenylic) and muscle (5-adenylic) acid in dogs In adequate doses, these substances produce a marked fall in blood pressure, accompanied by reduction in filtration rate ranging from 10 to 100 per cent depending upon the degree of blood pressure reduction Where the filtration rate is not too greatly reduced (0 to 35 per cent), the renal plasma flow remains constant or increases above the control value At lower pressures, renal plasma flow decreases In all cases the filtration fraction decreases Immediately after the infusion is stopped, the blood pressure and filtration rate return to or near the preinfusion level, and the renal plasma flow reaches hyperemic levels ranging from 111 to 240 per cent of the control, the hyperemia lasting for as long as 100 min The filtration fraction remains reduced Qualitatively similar results were obtained with yeast adenosine and sodium adenosine triphosphate The hemodynamic relations indicate an equal effect on the afferent and efferent arterioles.

CINCHONA ALKALOIDS

The fact that large doses of some of the cinchona alkaloids cause peripheral dilatation and a marked reduction in blood pressure led Hiatt and Suhrie [996] to examine their effects on the renal circulation in dogs In 14 out of 19 experiments, quinidine, cinchonidine, cinchonine, and quinine caused an increase in the PAH clearance of 30 to 50 per cent, the increase beginning within 30 min and lasting for several hours, according to the sojourn of the drug in the blood. The filtration rate also increased, but to a lesser extent It is presumed that these compounds act directly on the renal arterioles An increase of PAH clearance of 50 per cent or more can be maintained over a period of several days in normal

Bradley, Chasis, Goldring, and Smith [237] have shown that during the afebrile reaction (in premedicated normal subjects) the cardiac output generally increases, usually as a result of an increase in both the pulse rate and the stroke volume, while total peripheral resistance is decreased. Generally, these reciprocal changes are such that the arterial pressure is well maintained but, in some individuals, especially hypertensive subjects, the increase in cardiac

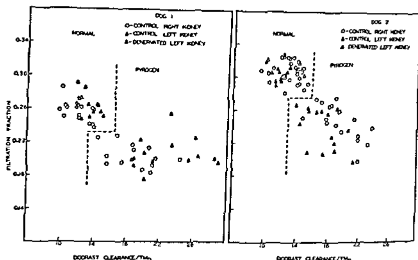


FIGURE 85. The filtration fraction in relation to the renal plasma flow per unit TmD in the intact and denervated kidneys of 2 dogs under normal conditions and during pyrexial hyperemia Each datum represents a clearance period (Hiatt [895])

output is inadequate to offset the decrease in resistance and arterial pressure is reduced, even to shock levels where it is necessary to keep the patient in a head-down position in order to maintain the cerebral circulation. At the peak of the reaction, most subjects show circulatory inadequacy, if placed in the upright position, owing to imbalance between cardiac output and peripheral resistance. In the recumbent position the renal fraction (per cent of cardiac output going to the kidneys) is increased, implying greater vasodilatation in the renal vascular bed than in the rest of the circulatory system.

Pyrexial hyperemia has been used to examine glomerular dynamics in normal persons [1934] and in subjects with essential hy-

circulatory picture closely resembles the early stages of shock prior t vasomotor collapse

Figure 87 shows observations made during the continuous intravenou infusion of sodium nitrite, a technique that proves more amenable tc control than inhalation of amyl nitrite. It will be observed that thc stronger infusion in the latter part of the test reduced the blood pressure but caused no severe circulatory disturbance. When, however, at

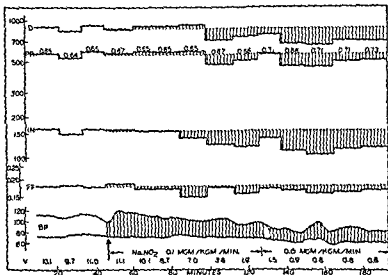


FIGURE 87. The effects of the constant intravenous infusion of sodium nitrite in a normal subject (Chasis, Ranges, Goldring, and Smith [114])

the conclusion of the last period the subject was raised in bed to 45 degrees, the blood pressure fell to 66/44 mm Hg and he complained of vertigo, demonstrating circulatory inadequacy

As the nitrite began to reduce the blood pressure, the renal plasma flow and filtration rate decreased, the latter to a slightly greater extent. In the last few periods there was marked oliguria perhaps related to the reduced filtration rate, although increased secretion of ADH cannot be excluded The renal response here is unlike that induced by adrenalin and presumably sympathetic excitation, in that the filtration rate decreased in a manner parallel with the renal plasma flow. This may be attributable in part to reduction in mean arterial pressure, but it is possible that the renal response involves dominant afferent constriction.

filtration fraction invariably decreasing Toxic manifestations are said to be relatively unimportant Blood pressure showed a definite reduction only in some hypertensive patients. The effects on renal hemodynamics are similar to those produced by pyrogen.

TETRAETHYLAMMONIUM

This quaternary ammonium compound has a marked sympatholytic action. Aas and Blegen [1] report that it reduces renal function in normal subjects The filtration rate decreased by 4 to 62 per cent (average −26.6), the renal plasma flow by 11 to 65 per cent (average −30.2) in 8 subjects receiving 100 mg/min of the drug by intravenous infusion The diastolic pressure was reduced in only 2 subjects, and the reduction in renal function appears to involve renal vasoconstriction, but perhaps of an autonomous nature. The drug also produced an acute reduction in urine flow, with some proteinuria. It is of interest that Page and Taylor [1568] have adduced evidence that this compound augments the vasoconstrictor action of adrenalin and other pressor drugs, as well as the depressor effects of isuprel, which pharmacologically resembles sympathin I.[426] Aas and Blegen caution restraint in using tetraethylammonium in conditions where renal vasular spasm may be present. There is no warrant to believe that, even if wholly effective as a sympatholytic agent, this compound would be effective in restoring renal function in anuria (ch. XXIV). Lyons, Moe, Neligh, Hoobler, Campbell, Berry, and Rennick [1256] report that the PAH clearance was not decreased during the hypotensive phase which follows its administration, although the filtration rate fell in a manner parallel with the blood pressure. From these and other observations on dogs, they infer that the compound produces some renal vasodilatation, but it must not be overlooked that the renal circulation autonomously tends to maintain itself in the face of reduced blood pressure, however produced, and a specific action on the kidney is not certainly indicated by these reports

SODIUM NITRITE

It has long been accepted, though on little evidence, that nitrites in general and sodium nitrite in particular lower the systemic blood pressure by dilating the arterioles However, Wilkins, Haynes, and Weiss [2220] have adduced strong if indirect evidence that sodium nitrite acts predominantly by dilating the venous system and reducing venous pressure; there follows a reduction of cardiac output and hence in arterial pressure, and the latter, acting through the carotid sinus-aortic arch receptors, induces vasoconstriction of the arteriolar bed The resulting

was followed in 15 to 20 min. by maximal diuresis, the average urine flow at the peak being 10.9 cc/min. above the control level.

In summary, the foregoing studies show that, while the renal circulation has considerable lability, the afferent and efferent arterioles have remarkable autonomy, or at least apparent autonomy, of action. However, most of the circumstances so far described as eliciting changes in renal function are rather extreme in nature, such as those that excite marked sympathetic activity and vasoconstriction elsewhere in the body. Clearly, whatever other regulation is imposed on the renal vascular bed, the renal circulation is subordinate to the emergency function of the sympathetic nervous system.

As opposed to this subordination, it may be reiterated that an outstanding feature of the renal circulation is the subtle capacity of the renal vascular bed so to adjust itself that the renal circulation tends to be restored in the face of prolonged increases or decreases in arterial pressure. The evidence indicates that this readjustment reflects autonomous activity which is independent of the vasomotor nerves, though that it is independent of extrarenal humoral agents cannot be stated One senses that this autonomous regulation actually acts in opposition to, or as a check upon, externally imposed vasomotor excitation, yielding only under extreme provocation, and that somewhere within the complexities of the renal circulation is a more subtle stimulus (or group of stimuli) which, because it is integral to the mechanism of autonomous control, can produce more immediate and profound changes in filtration rate and renal blood flow than are produced by most extrarenal factors. If we approach the problem of the control of the renal circulation with the *a priori* notion that this control consists of a balance of forces between opposing stimuli reaching the kidney from the outside, we are certainly destined to be disappointed. Despite certain limitations, the renal circulation performs a nicely quantitative job without the aid of the sympathetic nervous system, the adrenal medulla, the adrenal cortex (if adequate sodium is available), the neurohypophysis, or most of the other endocrine glands, and in doing so must make some remarkable readjustments of its own activitie

creased by 111 per cent. In a second, E_{PAH} averaged 0.925 before, and 0.89 when the renal plasma flow had increased by 53 per cent

It seems probable to the writer that the interpretation of Michie, Barker, and their coworkers, that large *rapid doses* of albumin open arterial-venous anastomoses, is the correct one. The problem is, however, a complicated one and will be discussed at greater length in chapter XXV.

Goodyer, Peterson, and Relman [812] report that the intravenous administration of 75 gm. of human salt-poor albumin into normal subjects during water and mannitol diuresis, which served to increase the plasma volume by 20 per cent as judged by hemoglobin and hematocrit, led to a reduction in urine flow, to a slight decrease in mannitol clearance (single injection method) (−11 per cent), to a decrease in sodium (−46 per cent) and chloride (−62 per cent) excretion, and an increase in potassium excretion (+40 per cent).

Venous pressure fell 15 to 60 mm. of saline in 2 subjects and rose 35 to 100 mm. in a third. A similar reduction in sodium excretion (from 3.0 gm. to 1.8 to 2.2 gm/day) occurred in a subject receiving 75 gm of albumin per day for 4 days, with no increase in urine volume. When albumin was stopped, sodium excretion returned to control levels. No albumin was excreted in the urine.

These negative results with respect to filtration rate and the decrease in sodium excretion contrast sharply with the increase in filtration rate and in salt and water excretion following the administration of albumin to patients in the nephrotic syndrome, where albumin infusion generally causes a large increase in filtration rate and sodium excretion (ch XXVI)

PLASMA

Lauson, Bradley, and Cournand [1217] did not observe any remarkable increase in renal function following transfusion of blood or plasma in patients in shock beyond what might be related to the improvement in the circulation. In most cases the renal blood flow remained at subnormal levels.

When large quantities (900 to 1955 cc.) of reconstituted plasma were given fairly rapidly to convalescent subjects who for the most part had normal renal function, Wilson and Harrison [2213] found a marked increase in the creatinine and PAH clearances, the filtration fraction invariably decreasing. (E_{PAH} was not determined.) The maximal increase occurred about 25 min. after infusion and

CHAPTER XV

Trophic and Other Factors Related to Renal Function

ANTERIOR PITUITARY

Numerous lines of evidence have long indicated that among the various trophic hormones elaborated by the anterior pituitary gland, one or more has a powerful renotrophic action. The kidneys of hypophysectomized rats weigh less than those of normal animals,[1363] and hypophysectomy prevents compensatory hypertrophy in uninephrectomized dogs[2202, 2247] and mice.[1363] Anterior lobe extract causes renal hypertrophy in castrate male mice, this effect being greatly enhanced by the simultaneous administration of thyroxin, although the latter has only a moderate effect alone,[1335] and such extracts inhibit the renal atrophy in rats which follows unilateral ligation of the ureter.[1336] The thyroid, gonads, and adrenals are not necessary for renal hypertrophy in rats, although hypertrophy may, for some unknown reason, be prevented by dietary factors.[670 933 934] Fontaine[670] inferred that renal regression in hypophysectomized rats is almost entirely the result of the decrease in endogenous protein catabolism, but this may be questioned since the renotrophic effects of anterior pituitary extracts are apparently not related to protein metabolism.

White, Heinbecker, and Rolf[2198 2203] have shown that functionally the dog kidney is very sensitive to the trophic action of the anterior pituitary gland. Denervation (or puncture) of the neurohypophysis in the dog results only in transient disturbances of renal function. The diodrast and inulin or creatinine clearances are slightly (10 to 15 per cent) increased after the operation, to fall slightly (20 to 25 per cent) below

Complementary to this speculative, almost intuitive, view is the fact that in some respects the kidney is charged with almost the sole responsibility for the regulation of the composition of the internal environment with respect to salt and water; and that, in carrying out this task, a nice balance must be maintained between glomerular and tubular function. The requirements of glomerular-tubular balance extend to the individual nephron, and thus one is tempted to the further speculation that what we observe in the mass action of the kidneys is but a statistical mean of many essentially autonomous units. There is evidence that here is at least one avenue (it need not be the only one) of approach along which we can search for the *vis a tergo* of renal regulation. The problem cannot be explored profitably except against a background of knowledge of electrolyte excretion, and further speculation can profitably be postponed to later chapters.

White and his coworkers early inferred that the thyroid and adrenal cortex were not directly involved in the trophic action of the anterior pituitary, and they attributed the change in renal blood flow and filtration rate to renal vascular changes and the reduction in Tm_D to a reduction in the quantity of some hypothetical transport substance in the tubule cells involved in diodrast excretion. Reduction in quantity of this transport substance would not necessarily reduce the extraction ratio at low plasma levels, but would reduce the maximal excretory capacity under load.[2199, 2200, 2202, 2203] The cardiac output in the dog is permanently reduced after hypophysectomy, to about the same degree as are the oxygen consumption and the renal blood flow.[2204]

Comparable depression of renal function as measured by Tm_{PAH} has been subsequently reported by White, Heinbecker, and Rolf.[2205] They affirm that this depression is not due to adrenal cortical regression, since adrenal replacement therapy adequate to maintain renal function in adrenalectomized dogs has no protective effect after hypophysectomy, and ACTH has no effect on renal function of hypophysectomized dogs ascribable to adrenocortical stimulation. Since the thyrotrophic and gonadotrophic hormones have been excluded, the essential loss in hypophysectomy is ascribed to some anterior lobe factor which acts directly on the kidneys.

More recently these investigators[2206] report that the renotrophic action is attributable to the growth hormone, which, administered daily for 9 to 12 days to normal dogs, doubles the PAH clearance and almost doubles the inulin clearance and Tm_{PAH}, while it raises the depressed values of hypophysectomized dogs to or above the normal levels. In view of the negative results obtained with the adrenotrophic and gonadotrophic hormones, and the slight effect of the thyrotrophic hormone, they attribute the principal effect to the growth hormone itself, or some substance not yet separated from it. The growth hormone, however, has but slight effect on renal function in adrenalectomized dogs maintained on DCA pellets, implying that its action, though not mediated through ACTH, requires normal cortical activity.

De Bodo, Earle, Schwartz, Farber, and Pellegrino (pers. com.) confirm the reduction in filtration rate and renal plasma flow in hypophysectomized dogs, and find that Tm_G is also reduced. Such animals respond to salt deprivation (intake 2 mEq/day for 3 weeks) in a normal manner in that urinary excretion of sodium and chloride are reduced to negligible values and the serum sodium shows only a minor decrease. Their tolerance to the acute intravenous administration of potassium is normal and excretion increases promptly to a level equalling or exceed-

normal at 4 to 6 weeks, with return to normal by 6 months. Tm_D may fall by 20 to 30 per cent within a few days of operation, but returns to normal within a few weeks and remains there permanently. White and his colleagues attribute these transitory disturbances of renal function to reversible damage to the pars distalis at operation.

Total (and simple) hypophysectomy,* however, resulted in a marked decrease in the inulin (or creatinine) and diodrast clearances, the former from an average of 104 cc. per sq. m. to 52.2 cc. by the fifth postoperative day, the latter from 237 cc. to 155 cc. E_D remained unchanged, being in the range of 0.71 to 0.85 before, and 0.70 after operation. Tm_D was also decreased, the loss in tubular function being even more striking than the reduction in circulation. Complete hypophysectomy reduced Tm_D from an average value of 21 mg. of iodine to 5.5 mg. 5 days later. There was no tendency to return to normal in 380 days. In 5 completely hypophysectomized dogs, the inulin clearance was reduced from an average of 104 cc. per sq. m. to 54.2 cc. on the fifth postoperative day; before and after simple hypophysectomy these figures were 80 and 54 cc.

Blood volume, as measured by T-1824 and calculated on the actual body weight, decreased by not more than 5 to 10 per cent during the first 6 weeks after operation; since the reduction in renal plasma flow and filtration rate occur much earlier, they were apparently not referable to decreased blood volume. There was no evidence of glomerular intermittence, as judged by White's[2192] injection method. Blood pressure (auscultatory) did not increase, but frequently both systolic and diastolic pressures decreased by 10 to 15 per cent 4 to 6 months after operation. Anterior pituitary extract markedly increased Tm_D in normal and 'puncture' dogs, and restored this function to or toward normal in hypophysectomized dogs, in which it is markedly reduced prior to treatment. It increased the diodrast and inulin clearances in all 4 groups.[946,2198] Comparable reductions in filtration rate and urea clearance in hypophysectomized dogs, but not in diabetes insipidus dogs, are reported by Pickford and Ritchie.[1616]

The urea clearance is increased in normal and diabetes insipidus cats receiving anterior lobe therapy.[625]

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stance was generally less effective They suggest that the action of thyroxin on Tm_D and Tm_G is effected by making more energy available through acceleration of phosphorylation, since thyroxin is known to accelerate the intestinal absorption of substances undergoing active absorption by a mechanism generally considered to involve phosphorylation However, possible effects of thyroxin upon the anterior pituitary are not excluded. Thyroxin does not increase the rate of tubular reabsorption of galactose [692]

Moustgaard [1293] reports that, although thyroidectomy resulted within 4 days in a 15 to 20 per cent decrease in renal plasma flow and filtration rate, it did not diminish the capacity of the dog kidney to respond with an increase in both functions on a high protein diet.

Thyroxin is known to cause an increase in renal weight in rats,[1149, 1329, 1830, 2029] but no data are available on the relative changes in different parts of the nephron Thyroidectomy does not prevent or reduce compensatory renal hypertrophy in the rat.[1365] The Addis urea excretion ratio varies with the BMR in patients with hypo- and hyperthyroidism, the correlation being better in the latter group.[1335]

ANDROGENIC HORMONES

Testosterone

Korenchevsky and his associates [1160] have shown that gonadectomy reduces the kidney weight in male rats but not in females, that androsterone and esters of testosterone produce hypertrophy of the kidney in both normal and gonadectomized female rats and in castrated males, and in large doses estrogens produce cyst-like degenerative changes in the juxtamedullary layer of the cortex. These renotrophic effects have been demonstrated in mice [1141, 1144, 1603, 1828] and the dog,[187, 2167] and confirmed in rats [1278] A number of such renotrophic steroids are now known; in a few (ex 17-methyl-androstanediol-3α, 17α) the renotrophic action appears to predominate over the androgenic action [1141, 1142] Testosterone increases the hypertrophy of the remaining kidney after unilateral nephrectomy,[1328] decreases renal atrophy after unilateral ureteral ligation,[1834] and affords some protection against mercuric chloride poisoning [1829] and the 'nephrosclerotic' action of DCA in rats.[1837] Unlike the renotrophic action of anterior lobe extract, the renotrophic action of androgens is not potentiated by thyroxin.[1338]

The renal hypertrophy induced by androgens is chiefly localized in the tubules In mice, the flat epithelium lining the parietal layer of Bowman's capsule undergoes marked thickening to the extent of be-

ing the filtered load. The excretion of water administered *per os* is, however, markedly delayed, only some 5 to 15 per cent of a dose of 40 cc/kg. being returned in 3 hr., whereas normally the return is 100 per cent.[491]

Oliver[1550] has pointed out that in compensatory renal hypertrophy in the rat the volume of some proximal tubules may increase fivefold, although the total kidney tissue increases only twofold. This trophic effect on the proximal tubule would appear to be related to the changes in Tm_D and Tm_{PAH} reported above.

The data available on man[96] are insufficient to indicate any consistent change in acromegaly.

THYROID

Thyroid in nontoxic doses causes enlargement of the adult rat kidney with hypertrophy of the tubule cells, while toxic doses cause atrophic changes[1149] The oral administration of thyroid increases the filtration rate in normal and diabetes insipidus dogs,[910, 914, 1624] and it increases Tm_D[946] and Tm_G[914] in normal dogs, and Heinbecker, Rolf, and White[946] have shown that it effects some restoration of Tm_D in dogs in which this function has decreased in consequence of simple or total hypophysectomy. Thyroid is, however, less effective in this respect than anterior lobe extract. It had only a slight positive effect in 'puncture' dogs, i.e. with a hypothalamic lesion causing diabetes insipidus and obesity. The diodrast clearance was not affected by thyroid treatment in the normal and 'puncture' dogs but increased substantially in hypophysectomized dogs, in which it was markedly reduced before thyroid treatment. The effects on the inulin clearance were positive but less striking

Thyroidectomy produces some decrease in the diodrast clearance and Tm_D, with little or no effect on the inulin clearance; the effects are far less than those of hypophysectomy, and the depressed renal function after hypophysectomy cannot be attributed to loss of the thyrotrophic hormone. Thyroid administration to thyroidectomized dogs raises the diodrast clearance and Tm_D, with slight effects on the inulin clearance As noted above, anterior lobe extract, which causes large increases in these clearances and Tm_D in normal and hypophysectomized dogs, produces small and inconsistent increases in thyroidectomized dogs, as in adrenalectomized dogs.[2204]

Eiler, Althausen, and Stockholm[591] have shown that thyroxin in massive doses (20 mg/day) increased the creatinine clearance in 3 dogs by 21, 42, and 45 per cent, Tm_G by 40, 29, and 56 per cent, and, in 2 of the 3 dogs tested, Tm_D by 115 and 48 per cent. The feeding of thyroid sub-

stance was generally less effective. They suggest that the action of thyroxin on Tm$_{D}$ and Tm$_{G}$ is effected by making more energy available through acceleration of phosphorylation, since thyroxin is known to accelerate the intestinal absorption of substances undergoing active absorption by a mechanism generally considered to involve phosphorylation. However, possible effects of thyroxin upon the anterior pituitary are not excluded. Thyroxin does not increase the rate of tubular reabsorption of galactose.[892]

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The renal hypertrophy induced by androgens is chiefly localized in the tubules. In mice, the flat epithelium lining the parietal layer of Bowman's capsule undergoes marked thickening to the extent of be-

coming cuboidal, and acquires brush border.[415,1823] Such cuboidal cells are present in small numbers in untreated mice, particularly during pregnancy.[445] Testosterone has no effect on the juxtaglomerular tissue.[19]

Castration does not produce any change in kidney weight in guinea pigs [1053,1144] and male Syrian hamsters,[1143] and in neither species do androgens cause significant renal hypertrophy.

Lattimer [1216] pointed out that the kidney in rats, cats, and humans tends to be slightly larger in males than in females, the sex ratio increasing to 1.5 in old cats.[859] He presents new data which give a kidney weight/body weight ratio in adult men (20 to 40 years of age) of 6 68 ± 0 17, and 5.99 ± 0.16 gm/kg in adult women. In male infants (80 per cent below 1 year of age) the male ratio was 10.2 ± 0.40 and the female ratio 9.99 ± 0.34 gm/kg He suggests that the male sex hormone increases the renal weight. He obtained evidence of renal hypertrophy in dogs treated with 10 mg/day of testosterone propionate for 32 days, and these observations led him to test this compound in man However, he obtained only insignificant changes in filtration rate and Tm_D in 2 normal men, 2 with essential hypertension, and 3 with only 1 kidney, treated with 25 mg of testosterone propionate intramuscularly daily for 14 days

In dogs again, Welsh, Rosenthal, Duncan, and Taylor [2167] found that testosterone propionate in doses of 100 mg daily produced a rapid rise in Tm_D, sometimes to the extent of a 100 per cent increase. This increased tubular function was reversible, but the time required for function to return to normal varied greatly. The creatinine and diodrast clearances were unaffected, as was the blood pressure But, in man, Taylor and his coworkers [1138] and Dean *et al* [481] found that 90 to 300 mg daily of testosterone propionate for periods of 8 to 29 days did not significantly alter the filtration rate, renal plasma flow, Tm_{PAH}, or Tm_G, 4 normal men and 5 patients with impaired renal function being tested In at least 2 subjects, the dose (300 mg/day) was comparable to that which had proved effective in dogs. A second androgen, pregnenolone, in doses of 100 gm daily for 30 days failed to influence the filtration rate, renal plasma flow, Tm_{PAH} or Tm_G in the 2 subjects tested.

The presumed efficacy of testosterone in the treatment of renal disease [1580] is problematic in view of these negative results Henderson, Seneca, Abd El Messih, and Weinberg,[976] however, report that the mortality in a cholera epidemic was substantially reduced by the administration of 25 to 50 mg. of testosterone propionate daily as a supplement to the established therapy. The authors attribute the beneficial effect in part to relief of oliguria and uremia. They note that albuminu-

ria decreased after therapy This interesting report presents several difficulties in interpretation, as do all problems involving the treatment of oliguria when recovery can occur spontaneously, but further studies will be awaited with interest.

ESTROGENIC HORMONES

Selkurt, Talbot, and Houck [1627] observed no significant changes in filtration rate in dogs receiving alpha estradiol benzoate, and the administration of this compound in doses of 4 to 6 mg/day in 4 normal women produced no consistent change in filtration rate, renal plasma flow, Tm_{PAH}, or Tm_G, although vitamin C Tm was reduced [431] as noted in the dog by Selkurt *et al* (ch. v)

Bilateral orchiectomy in 2 women had no effect on the filtration rate, renal plasma flow, Tm_{PAH}, or Tm_G,[431] and similar negative results with respect to the filtration rate and Tm_D are recorded in the dog.[2204]

Progesterone increases the urine output of both normal and hypophysectomized rats, the effect being most marked in terms of absolute diuresis in the latter, in which the urine flow may amount to 50 per cent of the body weight per day Resistance to water intoxication is increased in these animals [1832]

It is of some interest that Boettiger and Boettiger [201] report that estrogens are excreted by the tubules of the aglomerular fish, *Opsanus tau* Conjugation may be necessary before excretion is possible. If tubular excretion occurs in mammals, the assumption that blood and urine levels always run parallel may be questioned.

ADRENAL CORTEX

The action of adrenal cortical extracts and of DCA have been discussed in chapter XII

TROPHIC ACTION OF VITAMINS *

Vitamin A

Starting from the observations that, 5 to 7 hr after the ingestion of butter, the postabsorptive urea clearance in dogs may be increased by 45 per cent, Herrin and Nicholes [953] examined the non-saponifiable fraction of butter and cod liver oil and concluded that vitamin A was chiefly responsible for the functional change. Vitamin D was without effect.

* The term trophic is used here to designate the slowly developing increase in function which persists for some time after the exciting agent is withdrawn, in contradistinction to the rapid and transient functional changes associated with high protein diet, etc.

Supplementing a diet presumably containing sufficient vitamin A with 50,000 units daily in the form of halibut liver oil resulted in a 41 to 94 per cent increase in urea clearance, the earliest increase occurring within a week, the maximum after 96 days. In 1 dog, the clearance remained elevated for 44 days after the supplement was withdrawn. A dosage of 20,000 to 30,000 units daily reduced the variability in response and shortened the period required for maximal response. The larger dosage may have induced toxic effects. The urea clearance cannot be kept permanently elevated by the continued administration of vitamin A, the maximal observed duration of the effect being 87 days. The changes in urea clearance are paralleled by changes in inulin clearance, the urea/inulin clearance ratio averaging 0.537 during avitaminosis and 0.514 where the clearances were maximal as a result of vitamin A therapy.

Vitamin A deficiency decreased the urea clearance, which rose again to supernormal values near terminus. The depressed clearance rose in 11 to 50 days after the administration of 15,000 to 30,000 units of vitamin A (halibut liver oil or crystalline carotene) daily, the difference between low and high vitamin diets in most cases being of the order of 75 per cent. In rats, vitamin A deficiency caused a 23 to 77 per cent decrease in the urea clearance, without pathological changes in the urine or kidneys. Administration of carotene increased the urea clearance by 30 to 170 per cent over the level reached during vitamin deficiency[940]

In man, daily supplementation of the diet by 50,000 to 75,000 units of vitamin A (halibut liver oil or concentrate) produced no change in urea clearance in 2 subjects; in 4 subjects the clearance increased 11 to 15 per cent, and in 7 subjects the increase ranged from 24 to 91 per cent. This variability in response was not evident in dogs or rats. It is suggested that the individual with the greater amount of subcutaneous fat, who gains or loses weight easily, is the type who is most likely to respond with an increase in urea clearance In man, as in other animals, the elevated clearances begin to decline after a prolonged period of vitamin administration.[984]

Bing[171] found that doses of 5000 and 50,000 units per day of vitamin A in corn oil had no effect on the filtration rate, renal plasma flow, or Tm_D in dogs However, the daily administration of 200,000 units caused an increase in Tm_D or Tm_{PAH} in 3 out of 4 animals, the increase ranging from 50 to 100 per cent of the control value. Increased tubular function became apparent within 3 to 5 weeks. Only a slight increase was observed in Tm_D in a fourth animal. The filtration rate and renal plasma flow increased slightly in 3 out of 4 dogs, the filtration fraction remaining constant The effect of vitamin A differs, therefore, from that of

pyrogen or yeast adenylic acid, where the filtration fraction falls during renal hyperemia. Bing suggests that the increased renal plasma flow and filtration rate may represent a circulatory adjustment to the increased tubular function (an increase in renal weight not having been demonstrated).

Taylor, Corcoran, Schrader, Young, and Page[2053] studied the effects of vitamin A on man in relation to reported benefit in the therapy of essential hypertension. Of 2 normal subjects, 1 showed a 15 per cent increase in renal plasma flow; neither showed an increase in filtration rate, and the only one examined showed no increase in Tm_D. Of 10 subjects with hypertension, the renal plasma flow increased in 8, the range being from 0 to 110 per cent; the filtration rate increased in 6 (range 0 to 110 per cent), and Tm_D increased in 4 out of 7 subjects examined (range 0 to 95 per cent). In 3 subjects, the maximal increase in Tm_D was observed after treatment had been discontinued for 28, 21, and 30 days. There were no consistent changes in cardiac output (ballistocardiograph) The increase in Tm_D, the authors point out, may reflect an increase in the concentration of carrier substance in the tubule cells or an increase in cell mass, and, contrary to Bing, they suggest that the increased tubular function may be the result of prolonged hyperemia rather than a trophic action

Dicker and Heller[615] report that, in adult male rats on a basal diet containing 125 units of vitamin A per day, a supplementary daily dose of 250 units produces an increase in filtration rate, renal plasma flow, and Tm_D Free fluid occurred in the abdominal cavity in 9 out of 22 animals, a phenomenon never observed in control rats receiving the same water load.

Corcoran and Page[423] found that crude vitamin A concentrates, when given to rats in dosage of 2000 units per day intramuscularly, increased Tm_{PAH} by 100 per cent Crystalline vitamin A (2 mg/day) and neovitamin A (2000 units/day) were inactive. They conclude that the trophic action is not attributable to vitamin A, but to some other factor in commercial concentrates.

Vitamin B

There is some evidence that the capacity of the tubules to reabsorb glucose may be decreased in dogs suffering from deficiency of vitamin B[882]

Vitamins D and E

Herrin and Nicholes[933] found that the prolonged administration of vitamin D (irradiated ergosterol) and vitamin E (wheat germ oil) to dogs

was without effect on the urea clearance. A diet high in vitamin D decreased this clearance by 42 per cent and produced a urine which was dull reddish-brown in color and contained red and white cells and albumin, but no casts.

DIET

Jolliffe and Smith [1078, 1079] first reported that the urea clearance in dogs in the postabsorptive state (i.e. 18 hr. after the last meal) is considerably increased on a high protein (meat) diet as compared with a cracker meal (low protein) diet. The changes in the urea clearance are attributable to proportional changes in the filtration rate, as indicated by the creatinine or inulin clearances.[1865 1866, 2099] Though generally reproducible, the effects of a high protein diet in animals fed only once a day are far from quantitative, but all studies of renal function in dogs must be interpreted with due consideration of the maintenance diet.

The filtration rate may be increased nearly 100 per cent, 4 to 5 hr after a meal of raw beef, and it tends to persist at an elevated level for some hours so that the effect is cumulative. The maximal change, as between postabsorptive observations on a low protein diet and postprandial observations on a high protein diet, may be 3½-fold

The effect of meat protein can be duplicated qualitatively by casein, by the administration of thyroxin and phlorizin, both of which increase endogenous protein metabolism, and by the intravenous administration of glycine,* [66 1630, 1632] or the oral administration of glycine, glycylglycine, alanine, glycolic, and pyruvic acids, but not by glucose † [1624] Herrin *et al.*,[985] confirming the effects of protein, casein, and amino and hydroxy acids on the postprandial urea clearance, found that a similar effect was produced by lactic, acetic, and propionic acids, but not by gluconic acid. Benzoic acid depressed the clearance when the basal values were low, but markedly elevated it when the clearance was at an average level. Butter and the non-saponifiable matter of butter, when added to a meal of starch and lard, increased the average clearance by 45 to 57 per cent.‡

* In these experiments Pitts infused saline at a rate of 5 to 7 cc/min., which may have contributed to the renal hyperemia since saline is known to have this effect (ch. xi)

Glycine in amounts sufficient to raise the plasma concentration to 60 mg/100 cc is toxic and produces a decrease in renal blood flow and filtration rate, and an increase in the filtration fraction

† M. Friedman [701] reports that the oral administration of glycine does not increase the filtration rate or renal blood flow in the white rat.

‡ Vitamin A increases renal function in dogs, but the effect is rather more trophic than functional (*vide infra*).

Alpert and Thomas [43] showed that the urea, inulin, and diodrast clearances increase together, the inulin and urea clearances rather more than the diodrast clearance Normal, renal hypertensive, and neurogenic hypertensive dogs responded in a similar manner. Van Slyke, Rhoads, Hiller, and Alving,[2039] and Pitts [1632] showed that the increased filtration rate is accompanied by an increase in renal blood flow.

The most complete study of the effects of protein on renal function in the dog is that of Moustgaard,[1453] who has shown that, after a high protein meal, the inulin and hippuran clearance reach their maximal values at 3 to 6 hr , and return to normal by 24 hr. The effect on renal function is perceptible with 30 gm/kg of protein and reaches its maximum at 60 gm/kg when observed 4 hr after feeding The maximal increase in Moustgaard's experiments amounted to 80 and 70 per cent, respectively, in the inulin and hippuran clearances If protein is administered at intervals of 10 to 12 hr , these clearances do not return to low protein diet postabsorptive values, and the cumulative effect is such that postabsorptively they level off at about the maximal value reached 4 hr. after feeding, this maximum being reached on the third day. On return to low protein feeding, the clearances drop to initial values within 4 to 5 days

Moustgaard found that the intravenous administration of casein hydrolysate (5 cc/min of 8 per cent solution for 25 min) produces its maximal increase in the inulin and hippuran clearances (50 to 60 per cent) in about 100 min , the clearances do not return to normal in 8 hr. despite the almost immediate reduction of the blood amino acid to preinjection levels after the cessation of the infusion Moustgaard did not get increased renal function with the intravenous administration of lactic and pyruvic acids Increased protein intake had no demonstrable effect on glucose Tm, confirming the evidence from other sources that all the glomeruli in the dog are active However, the plasma glucose concentration at which saturation of the tubules occurred decreased as the filtration rate increased, as is to be expected

It is particularly noteworthy that Moustgaard observed no difference between the enervated and denervated dog kidney in this response to protein His studies on the effects of unilateral nephrectomy are recorded later in this chapter

The effects of protein feeding on renal function in man are in general less marked than in the dog Large variations in protein intake have been found to have almost no influence on the postabsorptive urea clearance in adults,[408, 801] although children appear to be more susceptible [623] The critical circumstance in man seems to be a very low protein diet;

Longley and Miller[1268] found that in normal adults the maximal urea clearance increases when the dietary protein is increased from 0.3 to 2.4 gm/kg per day, but no further increase occurs at higher protein intakes The administration of urea had no effect like that of protein These authors found that the urea and inulin clearances increased proportionally, the clearance ratio remaining unchanged. However, Nielson and Bang[1529,1530] report that on a low protein diet the urea clearance decreased 33 per cent while the inulin clearance decreased only 7 per cent, the diodrast clearance by 2 per cent. The observations on the two diets were made at essentially the same inulin U/P ratios, and the reason for the drop in the urea/inulin clearance ratio is obscure *

As compared with a light breakfast, a large protein meal (beef steak) had no effect on the renal plasma flow in 1 subject reported by White and Rolf,[2209] though it increased the filtration rate slightly. A high protein intake (220 gm/day) for a week raised the PAH clearance 18 per cent and the inulin clearance 31 per cent. Pullman, Alving, and Landowne[1662] kept 10 young adults on diets containing 0.3 to 0 4, 1 0 to 1.1, and 2.3 to 3 0 gm/day per kg of body weight, for successive 2 week periods. Eight subjects showed an increase in filtration rate, averaging 21.9 per cent on the high as compared with the medium protein diet. Seven showed a higher renal plasma flow, the average increase being 20.0 per cent. On the low protein diet, some subjects showed lower renal function as compared with the medium protein diet, but the differences were not significant. These authors also note that on a low protein diet the urea clearance decreases more than the filtration rate

On a low protein, low salt diet, subjects with essential hypertension show a slow decrement in filtration rate and renal plasma flow, these functions decreasing to about 65 and 80 per cent, respectively, of their control values, but the effect is clearly referable to the low salt intake, since both functions return to control levels on addition of salt to the diet.[355]

Moustgaard[1483] reports that, in the fasting dog, both the hippuran and inulin clearances begin to increase after the fifth day of the fast and by the twelfth day have risen some 10 to 20 per cent. Whether renal function is modified in man in consequence of prolonged undernutrition cannot be decided from the available evidence[1464]

The difference between man and dog in respect to the effects of dietary protein on the renal circulation is one of the most marked differ-

* This decrease may be related to increased proximal reabsorption of sodium and water. The urea/inulin clearance ratio has never been examined in man at various levels of glomerular activity.

ences in renal function between these two species.* It is paralleled by the equally great difference in the response of the glomerular circulation to the administration of saline (ch xi).

Dicker, Heller, and Hewer [619] find that in rats a protein deficient diet (carrots or turnips) maintained for about 36 days increases the filtration rate and renal plasma flow On the carrot diet, Tmp did not change significantly, but on the turnip diet it decreased from 0.132 mg iodine to 0 089/100 gm In contrast to normal animals, the filtration rate on the low protein diets was significantly correlated with urine flow. The low protein diets reduced the average maximal specific gravity from 1 070 to 1 041, and were accompanied by renal lesions.

Dicker [613] has further examined the effects of protein on the filtration rate in rats, with special reference to the relation of filtration rate to urine flow He finds that, in both young and adult rats, with a plasma protein concentration below 6 8 gm/100 cc the filtration rate increases with urine flow In adult rats fed on a diet containing at least 18 per cent casein and having a plasma protein concentration above 6 8 gm/100 cc, the filtration rate is independent of urine flow. Higher concentrations of protein in the plasma are accompanied by higher mean rates of filtration; rats fed an 18 per cent casein diet and having an average plasma protein of 6 83 ± 0 02 gm/100 cc. had a mean filtration rate of 0 43 ± 0 009 cc/min per 100 gm. body weight, while rats fed a 25 per cent casein diet and having an average plasma protein of 7 33 ± 0 026 gm/100 cc had a mean filtration rate of 0 76 ± 0 335 cc/min. per 100 gm body weight In both groups, the correlation between filtration rate and urine flow is slightly negative, whereas on diets of lower protein content in both young and adult rats the correlation is positive, the regression coefficient increasing as the protein content diminishes †

RENAL HYPERTROPHY ON A HIGH PROTEIN DIET

Addis, MacKay, and MacKay [20] first demonstrated that, when rats are placed for the first third of their life, beginning at 30 days after birth, on a high (70 per cent) protein (casein) diet, the kidneys undergo hypertrophy with no pathological change and no abnormalities in the urine. Enrichment of the diet with sodium chloride, calcium chloride (which

* Attention may be called to the fact that in the seal the phenomenon of diuresis is related to the assimilation of food, the urine flow increasing from oliguric levels to substantial values after a protein meal Here diuresis is attributable in large part to an increase in glomerular filtration (ch. xvii)

† It should be noted that the urine flow recorded here represents the spontaneous water intake and not water diuresis

is acidotic), or sodium bicarbonate has no *effect on kidney weight.*[21,1341] Hypertrophy does not result if the high protein diet is instituted after the animals have attained an age of 346 to 400 days.[1342] Urea, in quantities *equivalent to that excreted on the high protein diet*, has a slight hypertrophic effect, but it is less than that of protein,[1344] whereas no enlargement is observed in rats receiving repeated intraperitoneal injec*tions of urea solutions*[102] *or saline*[2010] Osborne, Mendel, Parke, and Winternitz[1658] found that lactalbumin was effective, and inorganic salts ineffective, in producing hypertrophy Evidence was obtained by these investigators that, after hypertrophy had been induced, some regression in kidney weight occurred if the animals were returned to a low protein diet.

The relation between protein intake and renal weight is a linear one An increase in a given percentage in the protein intake causes a larger relative and actual increase in renal weight in young rats because the protein intake per unit of body surface area for a given diet is much higher in young rats, while renal weight is essentially constant per unit surface area at all ages.[1328, 1331, 1332, 1337, 1339]

MacKay and Cockrill[1327, 1329] suggested that kidney weight is dependent on maintenance metabolism, and is almost directly proportional to endogenous protein metabolism on diets devoid of protein, but Wilson[2231] found that gelatin produces a greater increase in kidney weight than does casein or liver; glycine, glutamic acid, and gluten each produces an increase roughly proportional to the additional nitrogen consumed. Wilson believed that hypertrophy was associated with some stage in the intermediary metabolism of protein, probably deamination by the kidney. Feeding thyroid[1329] and phosphate[1341] also lead to renal enlargement.

A high protein diet leads to hypertrophy of the adult dog kidney when explanted under the skin. Such a kidney also shows increased size after a meat meal, and during saline diuresis.[39] Presumably hypertrophy occurs *in situ*, but it has not been demonstrated.

The increase in renal function brought about in the dog by a high protein diet is both too rapidly attained and too rapidly lost on a low protein diet to be attributed to hypertrophy, but must be conceived as primarily a functional effect.

Whether a high protein diet causes renal hypertrophy in man is unknown. Functionally the human kidney responds to dietary protein in a different manner than does the kidney of the dog and rat.

which follows partial nephrectomy.[349]

Baxter and Cotzias[102] obtained renal enlargement in young rats by the repeated intraperitoneal injection, over a period of 9 days to 2 weeks, of gelatin, human albumin, bovine globulin, and rat ser... e hypertrophy effected by gelatin bein... hyd...

...ast with globulin. Only ...cytologic changes, which consisted of enlargement and vacuolization of the cells of the tubules, the proximal segment being more markedly involved than the distal segment. Otherwise there was no evidence of renal injury and, except in one isolated group receiving gelatin, there was no formation of casts or dilatation of the tubules. The renal enlargement was readily reversible and the kidneys regressed to normal weight within 3 or 4 days after the injections were terminated The moisture and nitrogen content were not significantly changed, so that the increase in weight was apparently due to addition ... and water in nearly the ratio ...

In animals injected with ... bumin in the urine by serol... ...tion suggested that only a part, probably less than one-half of the urinary protein increment, was human albumin The remainder ... jected ...

...protein that accompanied ... of globulin The authors believe that the renal enlargement may have been caused in part by the injected protein molecules *per se*, perhaps by effects on the tubules of increased filtration of protein, rather than entirely by products of protein degradation

Since the intraperitoneal injection of casein hydrolysate does not produce renal enlargement, whereas casein administered in the diet does, it appears that the enlargement observed by Baxter and Cotzias is not related to protein metabolism, as in the case of a high protein diet generally

The authors conclude that prolonged continuous proteinuria under the conditions of their experiments, and of the degree obtained by them, does not lead to a persistent increase in glomerular permeability or to any form of chronic or progressive renal injury In the anomalous instances where tubular injury did occur (gelatin), the renal lesions resembled those seen in nephrotic kidneys The similarity between these lesions and those frequently seen in disease raises again the question whether some of the changes in the renal tubules frequently associated with intense proteinuria are secondary alterations resulting from exces-

sive amounts of protein passing through the glomerular membranes (ch. xxvi).

The proximal tubules in patients dying shortly after the administration of gelatin solutions as a plasma substitute show granular, finely vacuolated swelling similar to the hydropic changes which have been reported after large doses of sucrose These changes appear to be specifically related to the gelatin; they appear within half an hour after the intravenous administration of this substance and disappear within 120 hr. Pectin produces similar changes with pathologic implication.[1648,1907] The parenteral administration of all foreign proteins, no matter how apparently inert, is not *without danger of renal injury, especially if renal function is impaired, as it is apt to be under the circumstances where such proteins are likely to be used.*

COMPENSATORY HYPERTROPHY

It has long been known that atrophy of one kidney associated with unilateral renal disease is accompanied by hypertrophy of the contralateral organ. This hypertrophy can be accomplished experimentally by removal of one kidney (uninephrectomy) or by uninephrectomy plus removal of some fraction of the remaining kidney or various fractions of *both kidneys (subtotal nephrectomy). Uninephrectomy in man,* in the absence of disease on the contralateral side, is compatible with a normal life span.[1010,1168]

The increase in renal mass is attributable to hypertrophy and hyperplasia of the tubules, with swelling but no increase in number of glomeruli [56,1066,1471] Uninephrectomy during adult life in the white rat does not prevent the decrease in the total number of glomeruli that accompanies senescence [1474]

When experimental animals are maintained on a standard diet of moderate protein content, the remaining kidney after uninephrectomy *usually increases to about 75 per cent of the initial weight of the two* organs.[19] Addis' [14] data indicate that in the rat the increase in tissue, as judged by protein content, amounts to 50 per cent of the quantity of tissue lost, regardless of the latter figure. The hypertrophic process is independent of the nerve supply,[1377] and Morpurgo [1476] states that double nephrectomy in one of a pair of parabiotic rats caused hypertrophy of both kidneys in the other. No data are given, however.

Rollason [1740] concludes that hypertrophy following uninephrectomy begins in rats immediately after recovery from the shock of operation, maximal hypertrophy being reached within 20 days. Both cortex and *medulla increase in size, the latter to a lesser extent.* The tubules be-

come enlarged within 24 hr as a result of cellular hypertrophy, and on the second day increased mitosis reveals significant hyperplasia in all parts of the tubule other than the thin segment The glomeruli become enlarged in this species and in rabbits,[1769] primarily because of an increase in the size of the cells of the capsule and capillary tuft. Contrary to older views, he finds no evidence of an initial transient period of pseudohypertrophy (edema) Rollason believed that increased mitotic activity in the tubules is almost entirely restricted to the second day after operation, but Sulkin [2023] states that the peak of mitotic activity occurs between 72 and 240 hr after operation

Hypertrophy is greater in young than in old animals [1084, 1333, 1740] It is accelerated by a high protein diet and the ultimate increase in mass of renal tissue is greater.[14, 1323, 1336, 1918] Whole meat, extracted meat, whole liver, and extracted liver are about equally efficacious in promoting hypertrophy.[347, 348] In rats fed a standard diet (18 per cent casein), the remaining kidney statistically increases in weight by about 24 per cent within the first 3 weeks after uninephrectomy From the 21st to the 120th day there is a further steady increase at a slower rate, to the maximal increase of 48 per cent On a high protein diet (85 per cent casein) this hypertrophy is greatly accelerated and accentuated, the increase at the end of 3 weeks being about 60 per cent, a maximal increase of some 120 per cent being reached in 4 months These figures are relative to standard diet kidney weights and therefore include the sum of hypertrophy due to the increased protein intake plus the compensatory hypertrophy. The degree of hypertrophy is roughly proportional to the protein content of the diet Pathological changes are reported to be associated with the accentuated hypertrophy effected by a high protein diet [1457, 1915]

In subtotally nephrectomized rats raised on a moderate to high protein diet, the hypertrophy is most marked in the proximal tubule, this segment increasing in volume 5- to 10-fold, although the total kidney mass increases to only somewhat more than one-half that of the normal bilateral figure [14, 1680]

Bollman and Mann [204] believe that hypertrophy of the remaining kidney after nephrectomy is increased by the accumulation of urinary products in the blood following transplantation of the ureter so that the urine drains into the duodenum, but no control data are given.

Hinman [1010] states that, after partial nephrectomy on one side, both the untouched kidney and the fragment undergo hypertrophy, the incremeent being in proportion to their mass.

Compensatory hypertrophy does not occur after total hypophysec-

tomy, the anterior pituitary gland being necessary (*vide supra*) Thyroidectomy retards the growth of the kidneys, but it does not prevent compensatory hypertrophy of one kidney after uninephrectomy.[398, 1131, 1363, 2247, 2289] Castration is also without effect.[1326] Testosterone propionate accelerates compensatory hypertrophy in uninephrectomized rats and dogs.[1218, 1328]

Maluf[1377] reports that nephro-omentopexy reduces rather than increases function in the operated kidney, and it fails to prevent atrophy after subsequent division of the renal artery. After this operation, function in the contralateral kidney increases rapidly, maximal function being attained in about 2 months.

Water diuresis in rats from which one and one-half kidneys have been removed is at first greatly diminished but, within 4 weeks after operation, diuresis (as per cent of body weight per hour) recovers to about two-thirds of the control values. Forced water diuresis does not modify the normal weight of the kidney, the extent of hypertrophy, or the water content.

Using the venous sound method, Levy and Blalock[1231] found that uninephrectomy in dogs was followed by a slowly progressive increase in renal blood flow, somewhat more rapid in the first month, and reaching approximately the combined flow of the two kidneys at the end of 3 months.

Although earlier data on the urea clearance[23, 1092, 1703] are somewhat ambiguous with respect to increase in function, it is clear from these and other measurements that the ultimate increase in function is proportional to the increase in weight. The urea clearance ultimately increases after uninephrectomy to above 80 per cent of the two-kidney value in the rabbit[23] and dog[1092, 1703]

In one uninephrectomized rabbit, W. W. Smith[1947] obtained a filtration rate of 65 cc/min. and a diodrast clearance of 232 cc/100 gm. kidney weight, figures to be compared with her average normal values of 66.6 and 250. The single kidney weighed 15.3 gm. as compared with a mean weight of two kidneys in 5 other animals of similar size of 18.6 gm Thus, both function and size were about 80 per cent of normal

Moustgaard[1433] has shown that, 16 to 18 hr after uninephrectomy, renal function is at a level of 20 to 40 per cent of the original bilateral function, as judged by the inulin and hippuran clearances. During the next few days, function increases again to the preoperative value, after which it decreases a second time until after 2 to 4 weeks it reaches a steady level of 65 to 75 per cent of the preoperative value.

In the first phase of postoperative recovery, feeding protein does not

cause the typical increase in filtration rate and renal plasma flow, these functions already being maximal; but, as function decreases thereafter, protein again causes increased function, the maximal level attained after protein feeding increasing until some 3 weeks after nephrectomy when it levels off at about 65 to 70 per cent of the preoperative maximal postprandial capacity of the two kidneys. Tests carried out 11 to 16 months after uninephrectomy showed that both basal and maximal function had increased slightly, to a level of 72 to 82 per cent and 78 to 85 per cent, respectively, of the preoperative values.

Braun-Menendez and Chiodi [248] report that uninephrectomy in the rat reduces the inulin clearance and Tm_D during the first 20 days to 60 to 70 per cent of normal, these functions increasing to 80 per cent of normal after 3 months. Watschinger and Werner,[2181] however, report that after uninephrectomy the inulin clearance is reduced to half its normal value (from 0.58 to 0.28 cc/100 gm body weight) and remains(?) low (0.23 cc) up to the fiftieth day. The diodrast clearance by the fourth day was restored nearly to normal (normal 1.89, operated 1.75 cc/100 gm), as was Tm_D (normal 0.117, operated 0.123). Thus, the filtration fraction decreased from 0.30 to 0.16 and the C_{IN}/Tm_D ratio from 4.8 to 2.3. T_G (measured at plasma glucose concentrations of 267 to 326 mg/100 cc) decreased from 1.05 to 0.76 mg/100 gm, but at the reduced filtration rate Tm_G was probably not reached. These changes in diodrast clearance and Tm_D appear to have been completed by the fourth day after operation, but one may wonder if the number of observations is sufficient to establish this point. It is of particular interest that the average inulin U/P ratio in spontaneous urines decreased from 13.4 to 8.35, the urine volume in the normal and operated animals showing no significant difference.

Weiss and Chasis [2169] examined a patient with unilateral chronic atrophic pyelonephritis of the left kidney before and after removal of that organ. The right kidney was already slightly hypertrophic, as a result, no doubt, of atrophy of the pyelonephritic left kidney; functional data in the right kidney before nephrectomy were $C_M = 84$ and $C_D = 386$ cc., $Tm_D = 45.4$ mg. of iodine, $C_D/Tm_D = 8.5$, $C_M/Tm_D = 1.8$[illegible], $C_M/C_D = 0.218$. The left kidney had very little function: $C_M =$ [illegible] and $C_D = 56$ cc., $Tm_D = 3.0$ mg of iodine, $C_D/Tm_D = 18.7$, C_M/T[illegible] $= 5.67$, $C_M/C_D = 0.304$. Two and a half months after removal of [illegible] left kidney, the renal plasma flow had increased in the right kid[illegible] the function of which was now almost equivalent to two normal kid[illegible] $C_M = 96$ and $C_D = 593$ cc., $Tm_D = 48.4$, $C_D/Tm_D = 12.3$, C_M[illegible] $= 1.98$, $C_M/C_D = 0.162$.

Welsh, Wellen, Taylor, and Rosenthal [2169] report functional studies on 2 women in whom one kidney was removed, in one instance for persistent bleeding and in the other for adenocarcinoma No observations were made before uninephrectomy, and in the absence of control data the only change confidently indicated is a slow rise in Tm_D from 23 to 34 mg. of iodine within a year after removal of the functioning kidney in the first patient, with a corresponding decrease in the C_{IN}/Tm_D ratio.

Friedman, Selzer, Kreutzmann, and Sampson [712] examined 5 patients with essential hypertension and unilateral renal disease. The total diodrast clearance was reduced in 4 out of 5 of these patients, and in 3 examined by ureteral catheterization it was lower in the affected kidney than in the normal one. The total inulin clearance was subnormal in 2 and normal in 3 patients. The removal of the diseased kidney was accompanied by an increase in renal blood flow and filtration rate in all 5 patients, indicating that the remaining kidney had increased considerably in function.

Indications of increased filtration rate and Tm_D are reported by Lattimer [1216] in dogs with solitary kidneys treated with testosterone propionate. Two men who were treated during the period of compensatory hypertrophy (9 to 23 days postoperatively) after uninephrectomy showed some increase in filtration rate (11 and 28 per cent), and 1 showed a 39 per cent increase in Tm_D, the second only a 3 8 per cent increase in this function. Another postnephrectomy patient, in whom treatment was started on the twentieth postoperative day, showed a 7 per cent increase in filtration rate and a 22 per cent increase in Tm_D. These changes, of course, may have only reflected the process of hypertrophy.

Hogeman [1024] reviews the literature and gives data on 19 persons, 14 of whom had undergone nephrectomy 14 days to 23 years before study, and 5 had only one functioning kidney as judged by urography. The average inulin clearance was 77 cc., diodrast clearance 290 cc., filtration fraction 0.274, and renal plasma flow 520 cc. The data on inulin clearance alone indicate a significantly greater function in those operated on before rather than after the age of 30 years. These figures indicate a more moderate increase in function than do other data, but the statistical basis of comparison in subjects of widely different ages and with the potentiality of renal disease renders the comparison uncertain.

HEMIHYPERTROPHY

In a patient reported by Moore [1472] with hemihypertrophy (relative enlargement of the right kidney, right adrenal, right testicle, right lobe

of the thyroid, right cerebral hemisphere, and right half of the spinal cord), the right kidney weighed 195 gm. and contained 17,563 glomeruli/gm., the left weighed 150 gm. and contained 15,824 glomeruli/gm. The estimated total number of glomeruli in the right kidney was 906,251, in the left, 846,109. The enlargement of the right kidney had no significant effect upon the total number of glomeruli in the two kidneys.

OXYGEN CONSUMPTION

Van Slyke, Rhoads, Hiller, and Alving[2093] reported the first simultaneous determinations of oxygen and urea extraction by the kidney in normal, unanesthetized dogs, using the explanted kidney technique of Rhoads,[1702] by which blood from the renal vein could be obtained by needle puncture through the skin. The renal blood flow was calculated rom the urea extraction ratio and clearance. These authors review the xtensive literature on the oxygen consumption of the dog's kidney as etermined in anesthetized, operated animals.

The average renal blood flow in 11 experiments on 8 dogs with both dneys explanted averaged 4.0 cc/min. per gm. of kidney (range 1.9 7.4). In 13 experiments on 8 dogs from which one kidney had been noved at least one week previously, this figure was 6.7 cc/min. per of kidney (range 2.5 to 10.7). The oxygen consumption in the two- ey dogs averaged 0.08 cc/min. per gm. of kidney (range 0.03 to); in the uninephrectomized dogs this figure was 0.15 cc. (0.04 to . Thus removal of one kidney caused the blood flow to increase by y 70 per cent in the remaining kidney, while the oxygen consumption was nearly doubled when examined within a week or so after ne- tomy. In neither group of animals did diuresis correlate with renal flow or oxygen consumption, nor were these values affected by ministration of urea.

oxygen consumption correlated positively with renal blood flow, in general as the latter decreased the oxygen arterial-venous ce tended to remain constant at 2.5 cc/100 cc. of blood. The note that the renal venous blood in the dog is usually more per cent oxygenated, indicating that the kidney is kept under xygen tension than are most other organs.

the figures cited in chapter XVII and assuming a hematocrit of clearance method indicates a renal blood flow of 3.7 cc/min. f kidney, a figure which compares satisfactorily with the figure reported by Van Slyke *et al.*

tudies above, the urea clearance roughly paralleled the renal , E_u remaining generally independent of blood flow. E_u was

demonstrated to be independent of plasma concentration. This relationship also obtains when the renal blood flow is increased by a high protein diet.[2099]

The relative constancy of the oxygen arterial-venous difference (or alternatively of the extraction ratio), with consequent proportionality between oxygen consumption and renal blood flow, obtains in the dog during the renal ischemia attending shock until the blood flow falls below 1 cc/min. per gm.[531]

Mason, Blalock, and Harrison,[1416] using the venous sound method, obtained an average renal blood flow of 21.1 cc/min per kg body weight (range 16.0 to 29.8), a figure to be compared with 19.3 cc obtained by Van Slyke *et al.*[2098] After uninephrectomy, the renal blood flow in the remaining kidney increased by about 70 per cent, the oxygen consumption increasing proportionally and the oxygen arterial-venous difference remaining essentially constant.[1231] The average oxygen consumption in two-kidney dogs was 21.2 cc/min. per kg. of body weight (5.0 cc/min. per kidney).

In dogs rendered hypertensive by constriction of the renal arteries, the oxygen consumption parallels the renal blood flow, the oxygen arterial-venous difference remaining practically unchanged. Levy, Light, and Blalock [1232] estimate that in their control data the renal blood flow averaged 3.5 cc/min per gm of kidney; after application of the arterial clamps this figure was 2.7 cc. Levy *et al.*[1231] report that partial ureteral occlusion reduced the renal blood flow by an average of 41 per cent, without an increase in oxygen arterial-venous difference

Kramer and Winton [1155] studied the changes in oxygen consumption associated with acute changes in renal blood flow and other variables in the perfused dog kidney. In this preparation, as in the intact animal, the oxygen consumption paralleled the blood flow, and was only transiently modified by urea diuresis.

Weiss, Parker, and Robb [2160] obtained rénal venous blood by venopuncture in 3 normal subjects, and found an oxygen arterial-venous difference of 1.3 to 3 cc/100 cc. In a patient in the malignant phase of essential hypertension (nephrosclerosis), the oxygen arterial-venous difference was zero.

Warren, Brannon, and Merrill [2144] report a renal oxygen arterial-venous difference of 2.3 cc/100 cc (1.9 to 2.6) in 8 normal subjects examined by renal vein catheterization. The simultaneous systemic oxygen arterial-venous difference was 4.4 cc/100 cc. (3.7 to 6.1).

Cargill and Hickam,[329] in 10 normal subjects, found an average oxygen arterial-venous difference of 1.42 ± 0.25 cc/100 cc (range 1.09 to

1.87); the total renal blood flow averaged 1155 ± 229 cc/min. (range 835 to 1456), and the oxygen consumption averaged 16.0 ± 2.9 cc/min (range 12 to 20.8), or about 0.05 cc/min per gm. of kidney by estimated weight. They note that the normal renal oxygen arterial-venous difference of 1.42 cc/100 cc is notably small in comparison with accepted figures for mixed venous blood (4 cc/100 cc or more) and smaller than the recorded figures in the dog. The oxygen requirements of the kidney, which are relatively high per gm of tissue, are met by the large renal blood flow

Clark and Barker[333] find that water diuresis, mannitol diuresis, and saturation of the tubules with PAH have no effect on renal oxygen consumption in normal subjects Their normal average value, based on estimated kidney weights, is 6 1 ± 2 27 cc/100 gm kidney weight. Bucht, Werkö, and Josephson[259] also find that saturation of the tubules with PAH does not increase the oxygen consumption. Their data on renal oxygen consumption range from 7 to 13 2 cc/min, the oxygen arterial-venous difference from 0 85 to 1 90 cc/100 cc of blood

In 6 patients, studied by Cargill and Hickam, with essential hypertension in whom the filtration rate was above 100 cc, the oxygen arterial-venous difference averaged 1.30 cc/100 cc (range 0 82 to 1.51), the total renal blood flow 1008 cc (range 701 to 1237), the renal oxygen consumption averaged 13 2 cc/min (range 7 7 to 22 4). In 5 subjects with renal damage from hypertensive disease (nephrosclerosis) and filtration rates below 100 cc, these figures were 1 77 cc/100 cc, 487 cc and 8 1 cc As destruction of renal parenchyma proceeds, renal blood flow and oxygen consumption decrease without any marked increase in oxygen utilization.

In 6 patients with chronic nephritis or pyelonephritis, in whom the filtration rates ranged from 56 to 19 cc, these figures were 1 68 ± 0 20 cc/100 cc (1 30 to 1 90), 353 ± 176 cc (168 to 638), and 6 1 ± 3 3 cc (2 7 to 11 7) Here again, blood flow and oxygen consumption decrease in a parallel manner with no increase in oxygen utilization.

In marked contrast to the groups above, in 9 patients with acute or subacute glomerulonephritis who showed low (corrected) filtration fractions (mean 0 11 ± 0 03, range 0 08 to 0 16), the renal oxygen consumption was reduced to the average of 7 3 ± 2.5 cc/min (range 0 9 to 13 6) The oxygen arterial-venous difference averaged 0 71 ± 0 45 cc/100 cc (range 0 09 to 1 07), despite the fact that the renal blood flow remained normal or nearly so (average 1062 ± 179 cc., range 816 to 1362) This circumstance reflects either inability of the renal parenchyma to get oxygen out of the blood or a decreased metabolic demand.

Cargill and Hickam lean to the latter explanation and note that, considering all subjects examined by them, normal, hypertensive, nephrosclerotic, chronic and acutely nephritic, the renal oxygen consumption correlates with the filtration rate, implying that the load of material delivered to the renal tubules (for reabsorption) is the primary determinant of tubular metabolic activity. In this connection they quote Bradley and Halperin's [240] demonstration that oxygen consumption decreases with decreased filtration rate (and renal blood flow) during the ischemia induced by abdominal compression, and note that these authors suggested the possibility that renal oxygen consumption depends upon the relative proportion of tubular tissue actively functioning in the formation of urine from the glomerular filtrate. There are, as Cargill and Hickam recognize, alternative explanations, and this interesting idea must await substantiation No data are available to indicate to what extent oxygen consumption might correlate with active tubular tissue, as measured by Tm_{PAH} or Tm_G.

During abdominal compression, the renal blood flow, filtration rate, and Tm_D and Tm_G are substantially reduced in man,[240] apparently because the simultaneous elevation of renal venous pressure and intrapelvic pressure act respectively to decrease blood flow and arrest urine excretion from nephrons which have relatively low terminal intraluminal pressures Thus a large proportion of the renal parenchyma drops out of function. Under these conditions, the renal oxygen consumption drops from the control range of 6 to 14.2 cc/min. (average 10 3) to 1.2 to 9.3 cc/min (average 5.1) The oxygen arterial-venous difference is not significantly changed, so that oxygen consumption goes down roughly in proportion to the blood flow.

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GLOMERULAR-TUBULAR BALANCE 4

Since the individual tubule is fixed in size and, judging from the kidne as a whole, limited both in its reabsorptive and excretory capacities, i is a fair assumption that the quantity of filtrate delivered internally and the quantity of blood delivered externally per unit time are somehow conditioned relative to this fact Moreover, in so far as the peritubular blood in the mammals is derived from the postglomerular arterioles, tubular perfusion is dependent on continuing glomerular circulation The problem of glomerular-tubular balance therefore contains many important issues, ranging from the quantity of filtrate delivered to each nephron in relation to the reabsorptive capacity of the nephron for specific substances (sodium, water, glucose, vitamin C, etc), or the quantity of perfusate to each portion of the tubule in relation to its excretory capacity, to the questions of glomerular intermittency and the basic regulation of the renal circulation as a whole.

The supposition that the glomeruli in the mammalian kidney are intermittently active has been expressed repeatedly, with no supportive evidence. The idea stems from the observation of Richards and Schmidt[1715] in 1924 that only in some of the glomeruli of the frog, or in some of the capillaries in individual glomeruli, is the circulation active at any one moment, an observation which has been confirmed in other cold-blooded animals. In these cold-blooded forms the glomerular circulation can be increased by water diuresis and various drugs, notably caffeine, and decreased by splanchnic stimulation[28 156 162 897 1709 2156] In the frog,[874] the alligator (Shannon, unpubl obs), and the marine teleost fishes[898] the rate of glomerular filtration is more or less proportional to the rate of urine formation, the inulin U/P ratio varying through only a narrow range In the chicken,[1625 1885] however, and in most mammals studied this is not true (dog,[1860] cat,[2249] rat,[813 814] sheep,[1931] and man[363]) White[2192] concluded from injection experiments in the dog and rabbit that, where all the glomeruli are not injected, the unequal distribution is attributable primarily to differences in the patency of the larger, preglomerular vessels, rather than to inactivity of individual glomeruli, and that under normal conditions all the glomerular vessels are open

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the second part is not certain; in the marine seal, an animal entirely dependent upon its metabolic water for urine formation, both glomerular filtration and renal blood flow decrease during diving and increase markedly after the ingestion of food; these responses are, however, clearly adapted to an aquatic and salt-water life.[231, 995]

If one accepts the observations of Kaplan and Smith,[1090] Dicker and Heller,[514] Wilkinson and McCance,[2221] and Forster,[678] in the rabbit, glomerular activity increases or decreases with hydration or dehydration; if one accepts the observations of W. W. Smith,[1946, 1947] Brod and Sirota,[265] and Wills and Main,[2227] this relationship is a methodological artifact. Apart from the rabbit, the evidence is against glomerular intermittency in the mammals.

Smith, Goldring, Chasis, Ranges, and Bradley[1931, 1939] developed the glucose titration curve as a method of examining the variability of the ratio c_{in}/tm in the human kidney, where c_{in} is the filtration rate in an individual glomerulus and tm is the maximal glucose reabsorptive capacity in the attached nephron. As premises they accepted (a) that every tubule reabsorbs all the glucose presented to it by its glomerulus until the load is exactly equal to its maximal reabsorptive capacity; when the load exceeds this capacity, the excess glucose is excreted in the urine; (b) the status of individual nephrons remains unchanged during the period required for the completion of titration. Premise (a) excludes significant splay in the titration curve of an individual nephron. The method has not been developed further, in part because it seems unwise to extend either premise too far in respect to the diseased kidney, and glucose for technical reasons is not a suitable substance for this purpose. But the conclusions drawn by these investigators from their titration studies on normal subjects appear to be warranted. The data (see fig. 18) show that no appreciable number of nephrons have a glomerular activity (defined as c_{in}/tm) below 0.60 or above 1.5 times the mean glomerular activity (C_{IN}/Tm_G) for the entire kidneys; glomerular activity is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the nephrons fall within ±40 per cent of the mean. There is no large number of nephrons (i.e. the fraction is no greater than 5 per cent) in which glomerular activity is less than 60 per cent of the mean. Hence the notion of 'glomerular reserve' posited on the assumption of glomerular intermittency is untenable.

The conclusion reached by the glucose titration method is confirmed by the fact that Tm_G is not significantly modified by adrenalin, caffeine, or pyrexial hyperemia, all of which profoundly modify the renal blood

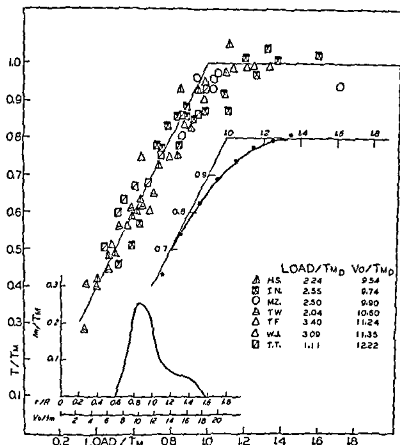


FIGURE 88 Normal dispersion of tubular perfusion Mass plot of diodrast titrations of 7 normal subjects, some of whom were titrated twice The mass plot contains 70 observations which were averaged by blocks of Δ load/Tm ≈ 0.1. The averaged data are shown in the inset, the smooth titration curve being drawn by visual approximation The limits of relative tubular perfusion are conformably placed at 0 66 and 1 66. The lower figure cannot be set with accu-

curve, and hence of the distribution curve, involves only a small percentage of the total tubular tissue.

As in the case of figure 18, the frequency distribution curve is practically identical with the normal frequency distribution curve The same qualifications

flow. That similar uniformity of glomerular activity exists in the dog is demonstrated by the extremely narrow range of plasma concentration in which tubular saturation with respect to glucose is effected, and by the constancy of Tm_G at various filtration rates effected by low and high protein diets,[1863] as well as by the narrow range of plasma phosphate concentration at which tubular saturation is effected and the fact that phosphate Tm is independent of the absolute value of the filtration rate [66]

Application to man of the titration principle with diodrast yields similar results: no appreciable quantity of tubular tissue has a perfusion rate (v_0/tm) below 0 66 or above 1.66 times the mean tubular perfusion (V_0/Tm_D) for the entire kidneys; the relative perfusion rate is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the tubular tissue is perfused at a rate within ±40 per cent of the mean (fig. 88)

On the basis of these data, it must be accepted that glomerular activity, defined relative to tubular activity in the attached nephron, is remarkably uniform in dog and man, and that changes in renal blood flow and filtration rate are the result of a fairly uniform increase or decrease in activity in all glomeruli. There is, therefore, no warrant for speaking of 'glomerular reserve' in the sense of inactive glomeruli or tubules.

Handley, Sigafoos, and La Forge [901] report that when the filtration rate is increased in dogs by the infusion of large quantities (amount not stated) of isotonic saline, Tm_{PAH} and Tm_G may be substantially increased. The C_F/Tm_G ratio remained constant in the one dog examined. Conversely, when dogs were dehydrated by the infusion of 20 per cent glucose solution with or without the use of mercurhydrin, Tm_{PAH} and Tm_G were reduced, the ratio C_F/Tm_G remaining constant in most experiments. Tubular function was not altered at the peak of diuresis (1 hr) but only after the urine output began to decline and sufficient water

must be applied to the massing of data obtained from different individuals as in the case of glucose titration Accepting the curve as drawn, it may be said

(Smith, Goldring, Chasis, Ranges, and Bradley [1931,1939])

had been excreted to produce moderate dehydration. The depressive effects increased with time as dehydration proceeded. The authors conclude that the changes in Tm_{PAH} and Tm_G represent changes in glomerular activity such as may be involved in the maintenance of fluid balance In the face of the evidence cited above, this interpretation cannot be accepted. Mudge and Taggart[1490] report no change in Tm_G in dogs after the infusion of saline, while the reduction in function during dehydration can scarcely be interpreted as physiological in view of the extreme degree of dehydration used in the experiments above. Modification of endocrine activity and of cellular activity by dehydration of the tubules are, moreover, not excluded.

ANOMALOUS EXTRACTION RATIOS

Van Slyke, Rhoads, Hiller, and Alving[2095] have reported that the oxygen capacity of renal venous blood when drawn by puncture of the renal vein of the explanted dog kidney is generally slightly less than that of the simultaneous arterial blood They attributed this to dilution of the renal venous blood by water absorbed in transit through the kidney. In view of the apparent uniformity of filtration and reabsorption of water, the explanation must remain suspect on a quantitative basis. In some observations the difference in oxygen capacity amounted to 1 to 2.5 cc/100 cc. (with a total oxygen capacity of 23 cc/100 cc), representing a dilution of renal venous blood by some 5 to 10 per cent, a discrepancy rather too large to be explained by water reabsorption

Mason, Blalock, and Harrison[1414] also noted that in some experiments the oxygen capacity of renal venous blood was as much as 1.5 cc/100 cc below the arterial capacity. Such differences in oxygen capacity occurred more frequently when the renal venous sample was obtained by puncture of the renal vein of dogs with explanted kidneys than when the sample was obtained by a venous sound.

Reubi and Futcher[1698] report that in dogs the oxygen capacity, hematocrit, and plasma protein content are higher in renal venous blood than in renal arterial blood, a difference which is increased by adrenalin. They suggest that this loss of fluid from the renal blood may occur through the renal lymphatic vessels or other vascular channels by-passing the renal vein. This difference does not obtain between femoral arterial blood (renal arterial blood is not available) and renal venous blood in man.

Van Slyke *et al.*[2095] also observed that in an occasional sample, the extraction ratio of urea might decrease to zero, or the renal venous

blood might contain more urea than the arterial blood. The phenomenon usually affected only one observation in a series. In such samples, however, the oxygen arterial-venous difference remained within normal limits They believed that the phenomenon was due to some reflex initiated by slight trauma connected with puncture of the renal vein, though they were unable to prevent it by cocainizing the vein. Gordon, Alving, Kretzschmar, and Alpert [819] similarly observed occasional concentrations of urea in renal venous blood equal to those in arterial blood in dogs with explanted kidneys

Such anomalous extraction ratios in the case of urea are not so surprising, since the normal extraction ratio is small (0.06) and back diffusion of urea might conceivably occur without corresponding loss of water or creatinine, though why it should occur in isolated samples of blood is not clear.

The phenomenon is less easily explained with inulin, diodrast, and PAH White [2193] reports that, in 1 out of 44 renal venous blood samples drawn from dogs with explanted kidneys, he found a higher concentration of diodrast and of inulin than in arterial blood On 2 occasions the diodrast extraction ratio was zero. He notes that, in 5 instances where extraction ratios below 0 40 were obtained, there had been difficulty in getting the renal venous sample. Apparent addition of diodrast to renal venous blood was also noted in a few instances by Corcoran, Smith, and Page.[428]

Warren, Brannon, and Merrill [2144] report 1 instance in man where, in renal venous blood (?) collected from the renal vein by catheter, the extraction ratio of PAH was zero, with an oxygen arterial-venous difference of such a size (2 4 cc/100 cc) as to indicate that the catheter had not slipped out of the renal vein In view of the non-traumatic nature of this technique, this result is more difficult to explain than low extraction ratios of urea in dogs with explanted kidneys, where compression of the renal veins and possibly of the ureter may be involved during puncture through the skin

Cargill and Hickam [329] were unable to confirm in man the observation of Van Slyke *et al* [2098] in the dog, that there is a difference in the hemoglobin content of arterial and renal venous blood. In man, 22 comparisons of oxygen capacity of paired, simultaneous samples showed a mean difference of 0 2 vol/100 cc, and 71 comparisons of paired hematocrit determinations showed a difference of 0 1 per cent packed red cell volume, differences within the limits of technical error. Breed and Maxwell (pers. com.) also find that in paired hematocrit determinations in ar-

terial and renal venous blood in man the maximal difference in packed red cell volume is no more than 0.1 per cent.

The anomalous extraction ratios reported above might be a consequence of the escape of urine from the renal pelvis into the venous system by pyelovenous backflow (ch. XXVI), but this explanation is merely speculative. They are recorded here for the sake of the record.

CHAPTER XVI

Renal Function in Infancy and Childhood

THE FETAL KIDNEY

In some mammals, such as the white rat, glomerular development is incomplete at birth, the kidney in the newborn containing numerous anlagen which continue to undergo differentiation, full glomerular development not being reached until the second or third month of life. After this time the glomerular count remains constant until regression begins with senility, roughly at one year of age in this species.[55, 1126]

In man, however, glomerular development is normally completed *in utero*. Cessation of the formation of new glomeruli is primarily dependent on the size attained by the fetus, and only secondarily on the gestational age. Formation of new glomeruli ceases ordinarily when the fetus weighs between 2100 and 2500 gm. and measures from 46.0 to 48.9 cm. in length. The kidneys of the majority of fetuses born before the beginning of the thirty-fifth week (from the first day of the last menstrual period) show the presence of incompletely developed glomeruli; in the majority of those born after the beginning of the thirty-fifth week, none are visible. In premature infants glomerular development continues after birth until the potential number of glomeruli has been attained. Potter and Thierstein [1651] accept the state of glomerular development as an index of fetal maturity.

In the adult human kidney, the glomerular capillaries are covered with the thinnest of epithelium, so that there is a minimal barrier to filtration. In fetal life the glomerular loops are matted together and invaginated into a sac of tall columnar to cuboidal cells,* which persist over the peaks of the capillary loops into postnatal life.[382, 830, 915] Transformation of the cuboidal epithelium to the squamous type begins in the juxtamedullary glomeruli and progresses toward the cortex, to reach completion within a few months to two years after birth. This is probably a gradual process, there being no evidence of an abrupt transformation at birth. The presence of this cuboidal epithelium in the visceral layer of Bowman's capsule probably seriously impairs filtration in the embryonic kidney and substantially reduces it in the newborn.[444, 915] The persistence of embryonic epithelium, together with unequal development of the glomeruli and tubules, leads to serious glomerular-tubular imbalance in young infants and poses perplexing problems for the pediatrician

At term, the tubules of the glomeruli near the capsule are still primitive and the loops of Henle are very short The juxtamedullary nephrons are more advanced, but even here the loops of Henle are not fully extended. When the growth (volume) of individual segments of the nephron in the rat is compared to the growth of the sum of its parts, it is found that the proximal segment grows most rapidly in relation to the whole.[1540] This possibly reflects the earlier and fuller development of the juxtamedullary region.

In the newborn rat, the cortex has a peripheral neogenic zone of undifferentiated tissue which is inactive, if judged by the storage of trypan blue, whereas the proximal tubules deeper in the cortex take up this dye in proportion to their age. Dye storage does not occur in the peripheral neogenic zone until 12 days, but by 28 days the peripheral tubules are fully developed. The vital storage of dye is correlated with the acquisition by the proximal tubule cell of brush border.[102] Proximal tubule tissue from the chick and human embryo, the latter from the second or third month of fetal

* Klein,[1129] in 1873, recognized that the visceral glomerular membrane in mature and immature human fetuses is composed of cuboidal to columnar cells, but he did not recognize that this circumstance is unique to the fetal period and not applicable to the mature kidney

life, when grown in tissue culture, secretes phenol red and, although such tissue possesses a rather remarkable capacity to undergo differentiation *in vitro*,[illegible] there is little doubt that it is capable of function in the fetus.

The mammalian kidney begins to function in the formation of urine to a limited extent before birth. The fetal bladder contains urine by the fourth month of gestation, this urine being discharged in great part into the amniotic fluid, which shows a progressive increase in urea and uric acid content, probably of urinary origin. The first rarely exceeds 50 mg/100 cc., possibly because of its diffusibility; the latter may accumulate to 40 to 50 mg/100 cc. The osmotic pressure of the amniotic fluid corresponds to $\Delta = 0.520$ at 2.5 months, 0.515 at 4.5 months, 0.482 at 7.5 months, and 0.467 at 10 months (plasma = 0.55).[881] This decrease in osmotic pressure indicates that it is to some extent osmotically isolated from both the fetus and mother, and may reflect the accumulation of fetal hypotonic urine.

In the fetal rabbit, cat, opossum, chick, and pig, both the mesonephros and metanephros function in the glomerular excretion of ferrocyanide and the tubular excretion of phenol red; the mesonephros and metanephros may function simultaneously, so that renal excretion is a continuous process uninterrupted by the degeneration of the former.[768,769] Wells and his coworkers [485,2185,2186] report that the fetal rat kidney excretes phenol red and responds with mild osmotic (urea) diuresis 16 hr. before term. Shortly before term, the urine was dilute, glucose-free, and showed a urea U/P ratio of 11.7 and a creatinine U/P ratio of 42. Williamson and Hiatt [2226] have shown that the kidney of fetal rabbits *in utero*, 3 to 4 days before term, excreted only traces of phenol red in 1 hr. after subcutaneous injection. When calculated as per cent of the test dose recovered from the bladder in 1 hr., excretion increased rapidly after birth, the rate of increase being about 5 times as great as the rate of increase in renal weight, so that at the end of 10 days of postnatal life dye excretion had increased 100-fold over the prenatal rate, while the weight had increased less than 20-fold. There was no appreciable transmission of dye across the placental barrier in either direction in 1 hr., although Lell and Liber [1224] report that 15 to 30 per cent of a test dose of phenol red injected into

parison cannot be improved upon at the present time.* For the calculation of surface area see chapter XVII.

MATURATION OF RENAL FUNCTION IN INFANCY

Numerous studies are now available on renal function from infancy to adolescence. The earliest of these, by Schoenthal, Lurie, and Kelly,[1798] indicated that the urea clearance in 9 normal infants 2 to 11½ months in age, when corrected to 1 73 sq m. of body surface area, agreed with the normal values reported by Van Slyke and his coworkers for older children and adults However, Barnett[90] found that the inulin clearance corrected for surface area is about 20 to 40 per cent of normal in infants 4 to 9 days of age, 50 to 90 per cent of normal at 14 days to 7.5 weeks, and essentially normal in children 6 to 10 years of age. The observation that the filtration rate in infancy is less than normal on a surface area basis has been repeatedly confirmed McCance and Young[1307] report an average value of 51 cc per 1 73 sq. m in 3 newborn infants; Dean and McCance[483] 27.2 (16 3 to 44 6) in 6 infants 2 to 8 days old; Barnett, Hare, McNamara, and Hare[92,93] 47.8 (34 8 to 65.9) in 13 premature infants 3 to 21 days old and 67 4 in 9 premature infants 49 to 107 days old; and Young and McCance[2254] 28 8 (9 5 to 61.8) in 7 full-term infants 1 to 8 days old who were possibly dehydrated from gastroenteritis Average figures are, however, not very meaningful since some of the variations are due to differences in water and electrolyte load. Moreover, it is clear from the data above and those of West, Smith, and Chasis[2175] and Rubin, Bruch, and Rapoport[1751] that, beginning at birth, the filtration rate † increases steadily throughout the first year. After this time it maintains essentially normal values.[90,235,1893,1751]

RELATION OF URINE FLOW TO FILTRATION RATE

McCance and Young[1307,2253,2254] believed that the inulin clearance increased with the rate of urine flow (i e. with the degree of hydration),‡

* This decision is affirmed despite Tanner's[2041] criticism of Houck's[1087] data on the dog.

† Both groups of investigators used mannitol to measure the filtration rate, but both used the periodate oxidation method of Smith, Finkelstein, and Smith[1946] for the determination of mannitol and, since, in the writer's experience, this tends to give higher mannitol/inulin clearance ratios than does the chromotropic acid method of Corcoran and Page,[424] no correction has been made for reabsorption of mannitol West *et al* used a constant intravenous infusion of mannitol and PAH, while Rubin *et al.* infused PAH but used a single injection of mannitol.

‡ A parallel has been drawn between the infant kidney and that of the rab-

of kidney weight is better with surface area than with height or body weight,[1325] the data of Vierordt [2112] and Wald [2124] indicating that this relation is maintained between 5 and 69 years of age. Kunkel [1177] concluded, from studies in several mammals, that the number of glomeruli are more closely related to body surface area than to body weight. Taylor, Drury, and Addis [2048] pointed out that the Addis urea ratio (60 min. clearance) is proportional to renal weight, and hence to body surface area, in rabbits, and McIntosh, Möller, and Van Slyke [1321] have shown that, after the age of 1 to 2 years, the urea clearance is proportional to surface area in children and has the same magnitude as in the adult, an observation which has been confirmed by Schoenthal, Lurie, and Kelly,[1798] Payne and Shukry,[1682] and Cullen, Nelson, and Holmes,[459] Cullen *et al.* reporting that the distribution and mean value of the urea clearance so calculated in 62 children, 5 to 13 years of age, correspond to those of normal adults. Holten [1029] showed that the creatinine clearance in 90 children from 9 months to 17 years of age correlated better with surface area than with body weight, and West, Smith, and Chasis [2175] accepted the surface area basis of comparison. Rubin, Bruch, and Rapoport,[1781] from data on 63 infants and children, decided that the filtration rate correlates poorly with body weight, body height, and calculated metabolic rate; when calculated kidney weight is used, there is a gradual increase in filtration per unit of kidney tissue, with stable ratios being reached between the fourth and fifth months of life; after this age the values more closely parallel the adult values than with any other method of reference; when body surface area is used, occasional adult values are reached around 6 months of age, but the values are not consistently in the adult range until about the second year.

Although kidney weight has much to recommend it, reference to a standard which not only has to be calculated but which itself has a large coefficient of variation (0.18) [2124] would seem to complicate the problem unnecessarily. Absolute values of various renal functions among adults of various ages, when expressed on a surface area basis, have fairly low coefficients of variation (ch. XVII), and this fact, coupled with the considerations stated above, leads the writer to believe that the surface area basis of com-

edly dependent on urine flow than in the adult, the urea/inulin clearance ratio decreasing from about 0.85 at an inulin U/P ratio of 10 to 0.3 or below at an inulin U/P ratio of 90 (fig 89). Barnett and his coworkers state that the clearance ratios reported by others conform with their data, and conclude that the urea clearance alone is without mean-

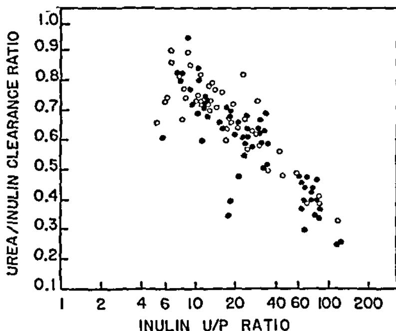


FIGURE 89. Urea/inulin clearance ratio in premature infants In adults this ratio has a value of 0 60 at an inulin U/P ratio of 10, and about 0.48 at an inulin U/P ratio of 100 (Barnett, Hare, McNamara, and Hare [93])

ing; it can be interpreted only when the filtration rate is known, for it is influenced, as in adults, by the filtration rate, by water reabsorption, and by the rate and direction of change of urine flow However, at moderate urine flows (inulin U/P ratio of 10 to 20) the average urea/inulin clearance ratio is about the same (0 5 to 0 6) as in adults.[93, 363, 1693] In older children, the urea clearance, like the filtration rate, comes up to the adult value.

West, Smith, and Chasis,[2176] and Rubin, Bruch, and Rapoport [1761] have discussed the changes in filtration rate, renal plasma flow, and Tm_{PAH}. Since it is agreed that by the age of 2 years all

a conclusion affirmed by Barnett, Perley, and McGinnis [95] from observations on a newborn infant with extrophy of the bladder, and by Dean and McCance.[483] Dicker and Heller (pers. com.) report that the filtration rate increases with urine flow during water diuresis in newborn guinea pigs, but not in adult animals. However, the studies of Barnett *et al.*[91, 93] on premature infants, hydrated and dehydrated, show a change in filtration rate of only 20 per cent between urine flows of 0.05 and 0.7 cc/min. (*c* 0.5 to 7.0 cc/min. per 1.73 sq. m.), indicating that there is no special lability of the glomerular apparatus in infancy. No obvious relation between filtration rate and urine flow is apparent in the data of West *et al.*[2175] or Rubin *et al.*,[1751] though these studies were complicated by the diuretic action of mannitol and were not made in dehydrated infants. In a more recent paper, Dean and McCance[485] recognize that, because of the osmotic limitations of the infant's kidney, the filtration rate may well determine the urine flow. As McCance[1298] notes, more information is needed on effects of dehydration on the filtration rate, for, if it is true that glomerular activity is readily reduced by dehydration in infancy, this fact would go far to explain the abnormal electrolyte pattern often observed in the first weeks of life.

UREA CLEARANCE

As would be expected from the low filtration rate, the urea clearance in the newborn is also below the adult figure when calculated on a surface area basis.[93, 483, 486, 1307, 1751, 2067, 2283, 2284] Gordon, Harrison, and McNamara[815] concluded that the 24 hr. urea clearance, which is lower in premature than in full-term infants, shows no relation to urine flow,* and the urea/inulin clearance ratio did not vary markedly with urine volume in the data of McCance and his coworkers[483, 1307] on full-term infants, or in those of Young, Hallum, and McCance[2283] on premature infants, because both clearances tended to decrease with urine volume. However, the data of Barnett *et al.*,[93] who studied the same infants during hydration and dehydration, show that the urea clearance is even more mark-

bit, but the reported decreased filtration rate at low urine flows in the rabbit, originally reported by Kaplan and Smith[1090] and confirmed by Wilkinson and McCance,[2231] Dicker and Heller,[514] and Forster,[678] has been shown by Brod and Sirota[246] to be in large part a 'physiological anomaly related to renal vasoconstriction elicited by excitement of the animal' (ch. XVII). According to Brod and Sirota, if rabbits are handled with due respect to their unusual psychic sensitivity, the filtration rate proves to be independent of urine flow down to very low values of the latter. The same may also be true of infants

* This may be because diurnal variations in glomerular activity nullify the effects of diurnal variations in water excretion.

figure of 23.3 gm. for the average kidney weight in the newborn, to obtain the ratio 0.26 cc/min. per gm. of kidney. In the adult, this ratio may be taken as 0.46 cc/min. (ch. XVII). Alternatively, on a surface area basis, the average filtration rate in the newborn

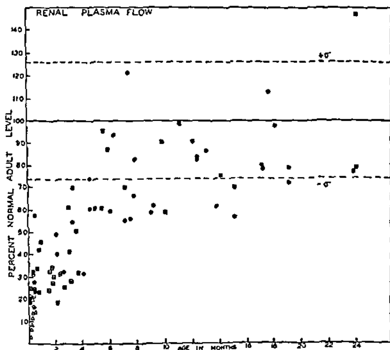


FIGURE 91 Renal plasma flow in relation to age in premature and full-term infants. Symbols as in figure 90

may be taken as no more than 50 cc/min. per 1.73 sq. m. (some observations are as low as 3 cc.[485]), which is to be compared with the adult figure of 127 cc. As noted above, the filtration rate increases to reach the adult value on a surface area basis generally by the end of the first year, and almost invariably before the end of the second year (fig 90).

Dean and McCance[183] obtained an average diodrast clearance of 66 (25.2 to 124.7) cc/min. per 1.73 sq. m. in 7 infants 2 to 8 days old. Barnett *et al*[32] report an average PAH clearance of 148.5 cc.

functions have generally reached adult values on a body surface area basis, data on subjects above this age will not be reviewed here. All data available to the writer have been collated in figures 90, 91, and 92, and the derivative calculations in *figure 93*.

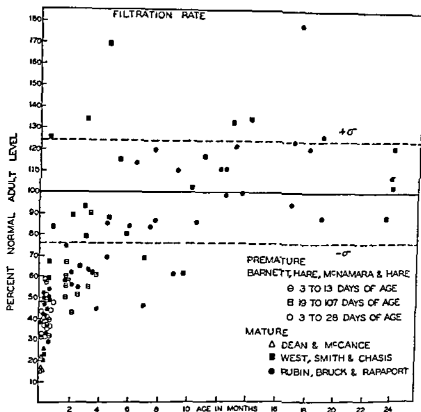


FIGURE 90. Filtration rate in relation to age in premature and full-term infants The data are drawn or recalculated from the authors indicated. The normal adult value is taken from table XII (mixed sexes).

As Rubin and his coworkers demonstrate, in agreement with the studies cited above, whether judged on a basis of kidney weight, body height, or surface area, the filtration rate is *relatively low in* the newborn infant. Their data on infants under 1 month of age average 0.20 cc/min. per gm. of calculated kidney weight; alternatively, we may divide the average filtration rate *of 6.0 cc.*, as indicated by the data of various observers, by Muhlmann's [1491]

figure of 23.3 gm. for the average kidney weight in the newborn, to obtain the ratio 0.26 cc/min. per gm. of kidney. In the adult, this ratio may be taken as 0.46 cc/min. (ch. XVII). Alternatively, on a surface area basis, the average filtration rate in the newborn

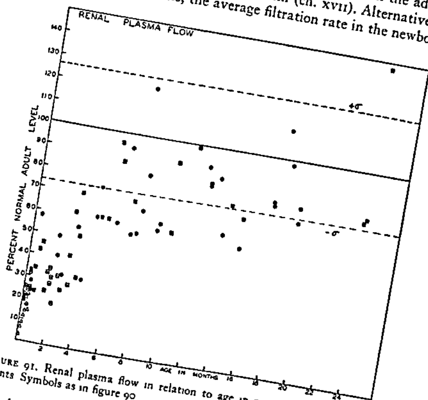


FIGURE 91. Renal plasma flow in relation to age in premature and full-term infants Symbols as in figure 90

may be taken as no more than 50 cc/min. per 1.73 sq. m. (some observations are as low as 3 cc [485]), which is to be compared with the adult figure of 127 cc As noted above, the filtration rate increases to reach the adult value on a surface area basis generally by the end of the first year, and almost invariably before the end of the second year (fig. 90).

Dean and McCance [441] obtained an average diodrast clearance of 66 (25.2 to 124.7) cc/min. per 1.73 sq. m. in 7 infants 2 to 8 days old. Barnett *et al.*[92] report an average PAH clearance of 148.5 cc.

in 8 premature infants 3 to 13 days old; in 9 premature infants 49 to 107 days old this figure was 200 cc. Similar low values for the PAH clearance in infancy are shown in the data of West *et al.* Rubin *et al.* (fig. 91). As in the case of the filtration rate, the P

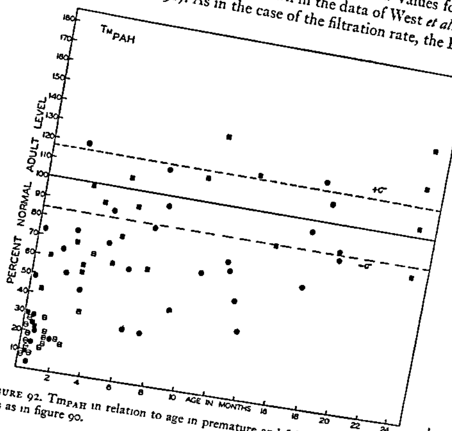


FIGURE 92. TmPAH in relation to age in premature and full-term infants Symbols as in figure 90.

(or diodrast) clearance increases to reach its adult value in many infants by 1 year of age, and in nearly all by the age of 2.

Tudvad and Vesterdal,[2085] in a preliminary abstract, report that during the first days of life the inulin clearance ranged from 12 to 14 cc. and the PAH clearance from 50 to 60 cc. per 1.73 sq. m. The filtration fraction was high (0.22 to 0.55). This value was 0.60 to 0.84 in 1 Mongolian idiot, indicating a high degree of immaturity of the kidney. Galan, Peréz-Stable, Martin, and Faéz [735] report an average diodrast clearance of 695 ± 183 cc., with the normal

filtration fraction of 0.19, in 3 children 8 to 10 years old; the C_{IN}/Tm_D ratio in 2 of these was 3 58 and 2.45, all data within the normal range.

The filtration fraction in Dean and McCance's [482] data averaged 0.427 (0.296 to 0 700); if two exceptions, both 0.70, are excluded, this ratio ranged from 0 30 to 0.47 and averaged 0.38. Because of this high value, they inferred that diodrast is incompletely removed from the renal blood. In the data of Barnett *et al.*[92] the filtration fraction averaged 0.34 in premature infants ranging up to 107 days old As shown in figure 93, the filtration fraction, high initially, decreases and is generally normal at 1 year of age.

As with the filtration rate and effective renal plasma flow, Tm_{PAH} has very low values at birth, but increases rapidly. West *et al.*[1176] believed that normal values were reached by about 30 weeks; a wider scatter is present in the data of Rubin *et al.*[1151] and, while several infants had attained adult values within the first 6 months, there were some in whom this had not occurred at 7 years (fig. 92).

It appears from the relationships above that various aspects of renal function are adjusted at an early age, usually under 1 year, to the metabolic requirements of the body, using the surface area as an approximate index of general metabolism. However, in this readjustment glomerular and tubular function develop at different rates, as is revealed by the changes in the derivative ratios (fig. 93). The problem is to relate this differential functional development to the anatomical development of the kidney.

First, we may consider the possible causes of the low filtration rate at birth. Excluding back diffusion of inulin or mannitol, this low filtration rate might be due to (a) low blood pressure, (b) increased afferent glomerular resistance and resulting low glomerular pressure (which would be accompanied by a low blood flow), and (c) the impediment to filtration offered by the cuboidal epithelium of the fetal-neonatal glomerular membranes.

The changes in blood pressure that occur at birth and during the first year of life are not too well known. The establishment of the adult circulation involves the obliteration of the placental circulation and the functional separation of the systemic and pulmonary circulation It would be expected that the latter process would be

accompanied by substantial and rapid increases in systemic arterial pressure, but such does not appear to be the case. Observations on experimental animals throw little light on the situation in

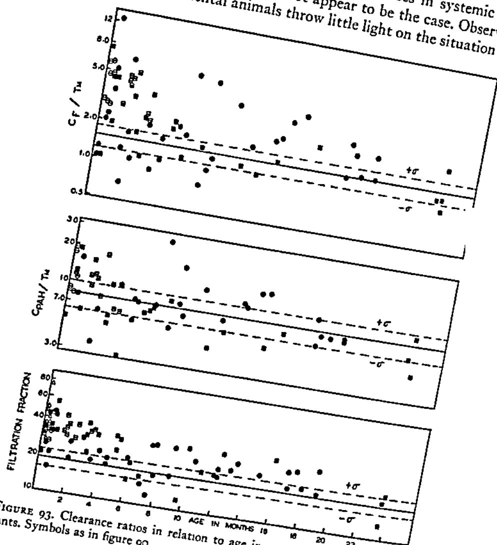


FIGURE 93. Clearance ratios in relation to age in premature and full-term infants. Symbols as in figure 90.

man for, in the dog and rabbit at least, the ductus arteriosus has a valve-like structure which is competent to stop the backflow from aorta to ductus, and after the ductus has been functionally closed for a while adhesions form and the closures usually become

anatomical. In the human fetus there are no valve-like flaps to guard the aortic opening of the ductus; what causes the aortic-ductus flow to stop and the ductus to close is an unanswered question.[391] Whereas closure occurs within a few minutes after delivery in most animals, the process is apparently more leisurely in man. However, an interval longer than 3 hr. is rarely required for the transformation of the fetal circulation into the adult circulation, as judged by the oxygenation of the arterial blood, and it may be much less.[1914]

Citing the data of several investigators, C. A. Smith [1914] gives the pressure in the umbilical artery in infants at the time of premature birth at 5, 6½, 7, 8, and 9 months as 33/21, 55/25, 70/35, 85/45, and 80/46 mm Hg, respectively, i.e. the systemic pressure rises toward its postnatal level throughout fetal development. The umbilical pressure immediately after birth averaged 80/46 mm. Hg in 24 normal infants studied by Woodbury, Robinow, and Hamilton.[2272] From these and other data, Smith concludes that the systolic pressure increases about 10 mm during the first 24 hr. of life and by another 10 mm between the first and fourteenth days, with a further increase no greater than 2.5 to 5 mm. during all the rest of the first year It therefore seems unlikely that the continued increase in filtration rate throughout the first year or more of life is related to increasing systolic pressure.

Given adequate blood pressure, a low filtration rate per gm. of kidney might be attributed to a paucity of glomeruli, but full-term human infants apparently have all the glomeruli they are ever going to develop The rate of filtration in these glomeruli would, however, be reduced by either exaggerated afferent arteriolar tonus or persistence of fetal glomerular membranes. In the first case the total renal blood flow would be low; in the second case, the total renal blood flow would be low only if the cuboidal visceral epithelium compressed the capillaries to such an extent as to impede perfusion.

The effective renal plasma flow, as measured by the diodrast or PAH clearances, is in fact lower at birth, relative to adult values, than is the filtration rate, as is shown by the supernormal filtration fractions recorded by all investigators (fig. 93). Nothing is known about the extraction ratios of these compounds in the in-

fant kidney, and in the absence of this information we can only indulge in speculation. That the high filtration fraction is attributable to a low extraction ratio is indicated (though not firmly established) by inference. The infant's blood pressure is below rather than above the adult value, and, even without excessive

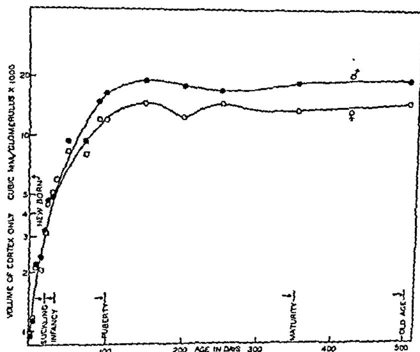


Figure 94. Growth of renal cortex (volume) per glomerulus in the white rat. (Recalculated from Arataki [16])

afferent arteriolar resistance, it may be surmised that glomerular pressure is also low; the persistence of fetal glomerular membranes *and the fact that the glomerular capillaries are typically under-*developed would also decrease rather than increase the filtration *fraction. Thus, with all these circumstances operating to reduce* the filtration rate per unit of total renal blood flow, it would seem that a high filtration fraction could only be the result of deficient tubular clearance of postglomerular blood. The most likely reason for deficient tubular clearance would be that some of this blood, after leaving the glomeruli, escapes into the venous circulation

without being presented to functional proximal tubular tissue. That such is probably the case is indicated by certain features of renogenesis. In early fetal life the medulla, at this stage bearing a large proportion of collecting tubules, develops ahead of the cortex. By the fourth fetal month, the renal tubules begin to differentiate into a thin descending and a thick ascending limb, the long loops extending downward and reaching the papillae by the fifth month, thus contributing to the increased depth and thickness of the medulla. While the medulla is increasing its transverse diameter by 100 per cent, the cortex increases only by 20 to 25 per cent.[633]

Development of the cortex proceeds from the juxtamedullary regions toward the capsule, with progressive elongation of the cortical tubules. This tubular development involves a gross readjustment between glomerular and tubular function, which can best be illustrated in the white rat, the only species in which detailed data are available. From the counts of Kittelson[1114] and Arataki,[55] it appears that the number of fully developed glomeruli increases by nearly 3 fold after birth, the maximal number not being reached until about 100 days. This fact implies that a number of nascent nephrons in the newborn rat are functionally aglomerular, even as all nephrons are functionally aglomerular in the early embryonic period. In addition, however, tubular tissue is developing even more rapidly than glomeruli. Indeed, despite the presence of incompletely differentiated glomerular anlagen in the newborn animal, the extent of tubular development is so meager that one may say (relative to the adult relations) that the kidney is predominantly glomerular.

This imbalance between glomerular and tubular development is well illustrated by Arataki's[55] classical studies. This investigator made glomerular counts and other measurements on the kidney in pairs (1 male and 1 female) of rats from birth up to 500 days of age. The writer has recalculated some of his data for presentation in figures 94 and 95. Figure 94 shows the volume of renal cortex * in cu mm. per (completely formed) glomerulus in

* This figure is the volume of cortex after fixation, as calculated by microscopic enlargement and planimetry of every other section (20 to 25 μ). Correction for shrinkage would not significantly alter the relations shown.

relation to age; since the glomeruli themselves represent only a small fraction of thé volume of the cortex, the latter can be taken to indicate the quantity of tubular tissue per nephron. The notable feature of these data is that between birth and 100 days the

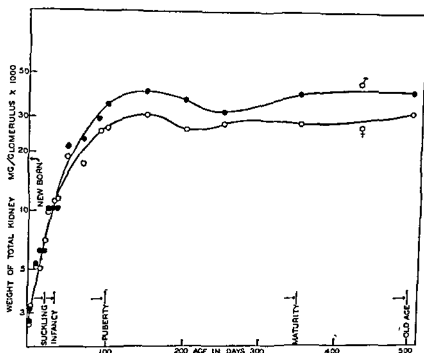


FIGURE 95 Growth of total kidney (weight) per glomerulus in the white rat. (Recalculated from Arataki [65])

quantity of tubular tissue per nephron increases 20-fold; since the tubules do not increase in diameter (fig. 96), this increase can only be effected by elongation of the proximal and distal tubules in each nephron. The same conclusion is reached if one calculates the weight of total kidney tissue per glomerulus (fig. 95).* The two methods of calculation yield essentially the same result because the relative proportions of cortex and medulla (the latter con-

* By both calculations, the adult male has slightly more tubular tissue than the female.

stitutes about 30 per cent of the total kidney volume) are practically constant in Arataki's data from 3 days on.*

As shown in figure 96, the average glomerular diameter increases by a little less than 100 per cent between birth and 100 days, but, even if this is accompanied by doubling of glomerular

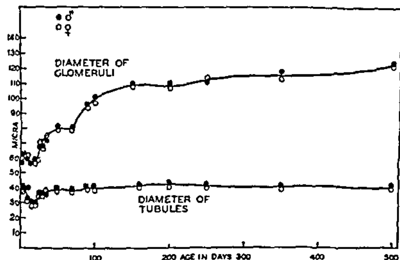


FIGURE 96. Changes in diameter of glomeruli and tubules in the white rat in relation to age. (Arataki [88])

function, in the kidney of the newborn rat glomerular function predominates over tubular function by a ratio of some 10 to 1 because of incomplete elongation of the tubules.† In man an increase in glomerular diameter is evident before the age of 1 to 2 years (table IX).

* In Kittelson's [1134] data, the volumetric ratio of medulla to cortex is 1:3.05 at birth, decreasing to 1:1.2 at 12 weeks and increasing again to 1:2.87 in the adult.

† Arataki notes that, as between 350 and 500 days of age, the total number of glomeruli in the kidney decreased from above 30,000 to some 20,000; since the diameter of the tubules and the number of glomeruli per unit volume of cortex remain constant, he concludes that the tubules of the disappearing glomeruli have also been destroyed, i.e. there is no evidence here of the formation of aglomerular nephrons in the senescent kidney.

In the newborn infant, the ratio of the height of the medulla to that of the cortex is about 1:5, in the adult this ratio is about 1:2.4, this proportion being closely approached between the first and second year.[2112] In the cat (no measurements are available in

TABLE IX

The Midsize of the Peripheral and Central Glomeruli in Man, in Micra

(After Kulz, cited by Arataki [56])

Age	Peripheral glomeruli	Central glomeruli
0 days	99	138
9 days	97	135
2.5 months	107	139
5 months	110	138
7 months	121	140
9.5 months	129	139
1¼ years	132	143
2¼ years	157	158
12 years	192	192
16 years	231	229
18 years	213	219
23 years	237	237

man) the relative expansion of the cortex involves a considerable elongation of the proximal tubule relative to the rest of the nephron. According to Sperber,[1869] the proximal tubule constitutes about 30 per cent of the total nephron length in the 12-day-old kitten, some 30 to 35 per cent in the young female cat, and about 45 to 50 per cent in the old male.

That tubular excretion could be carried on by proximal tubule tissue as rapidly as it develops is implied by the demonstrated activity of embryonic mesonephric tissue in *in vitro* cultures, and *during its development the proximal tissue of the cortex must* have a reasonable supply of blood, no doubt of glomerular origin. It is, however, conceivable that the peritubular capillary plexus is inadequate to present all postglomerular blood to proximal tissue because of incomplete relations between the peritubular capillaries and the rapidly developing proximal tissue; more particularly, the postglomerular blood from the juxtamedullary glo-

meruli, the earliest to develop, may be significantly deficient in this respect.

If the extent of development of proximal tubular tissue may be judged by Tm_{PAH}, the kidney of the newborn is very deficient in this tissue. Tm_{PAH}, like the effective plasma flow, is relatively lower at birth than is the filtration rate, as shown by the supernormal values of the ratio C_{IN}/Tm_{PAH}. The data of Rubin *et al.* indicate that in 7 infants 7 to 22 days of age Tm_{PAH} has a value of 0.10/gm of kidney; using Muhlmann's figure of 23.3 gm. gives a value of 0.13. This figure in the adult may be taken as 0.300 (ch. XVII). Thus, as functionally measured, there is only one-half as much proximal tissue per unit of weight in the kidney of the newborn as will be the case at 2 years of so Either (a) proximal tissue is present but is so poorly perfused by blood that it is not saturated in clinical determinations, or (b) this proximal tissue has not yet developed in proportion to kidney weight or filtering surface. In respect to (a) it has elsewhere been argued (ch. XIX and Smith,[1939]) that every unit of proximal tissue which is active in clearing PAH at low plasma levels must be conceived to be available to blood during the measurement of Tm_{PAH}; i.e. the two terms, C_{PAH} and Tm_{PAH}, have reference to the same excretory units and the same vascular channels Since the ratio C_{PAH}/Tm_{PAH} is normal or slightly high at birth (fig 93), such proximal tubule tissue as is clinically available appears to be normally vascularized and perfused, and we are thus led to reject (a) in favor of (b), namely that proximal tissue is not yet fully developed; the renal circulation at the start is predominantly a glomerular one, the postglomerular blood escaping into the venous circulation without tubular clearance because adequate tubular tissue is not there. This circumstance will lead to a low extraction ratio of diodrast and PAH, to low clearances of these compounds, and to a high filtration fraction. Thus all the facts are at least compatible with a low extraction ratio of PAH.

The supposition above is supported by the data of Williamson and Hiatt [2226] on the rabbit, in which the rate of excretion of phenol red per gm. of renal tissue increases 5-fold in the first 10 days after birth. If this is entirely a matter of increased renal blood flow per gm. of kidney, it requires a greater acceleration of glomerular de-

velopment than is indicated by the anatomical data on other species or by data on the functional activity of the glomeruli in man, whereas the observation conforms with the interpretation that after birth a predominantly glomerular circulation with poor tubular clearance is rapidly transformed by the continuing development of proximal tissue into one in which the postglomerular blood is fully distributed for tubular clearance. With this redistribution, C_{PAH} and Tm_{PAH} increase, roughly in the same proportion, and the filtration fraction falls. These changes are superimposed on a simultaneous increase in the filtration rate promoted by opening up of the glomeruli and regression of the fetal glomerular epithelium.

In brief, then, an interpretation that will fit all the facts is about as follows: glomerular development outruns tubular development *in the late stages of fetal life so that, at term, the kidney has its full complement of glomeruli but a deficient quantity of proximal* tubule tissue. Although the blood pressure is essentially normal, the filtration rate per gm. of kidney is low at birth because of impedance of filtration by the fetal epithelium. But, despite this functional deficiency in glomerular activity (i.e. relative to the *number* of glomeruli present), the circulation is predominantly a glomerular one because of a greater deficiency in development of proximal tissue, and considerable postglomerular blood escapes tubular clearance, these circumstances leading to (a) a low filtration rate per gm. of kidney, and (b) low values for E_{PAH}, C_{PAH}, and Tm_{PAH}, and high values for C_{IN}/Tm_{PAH} and C_{IN}/C_{PAH}. As *proximal tissue develops in the first year or so of life,* all postglomerular blood comes ultimately to be presented to proximal tissue for clearance and E_{PAH}, C_{PAH}, and Tm_{PAH} increase, while C_{IN}/Tm_{PAH} and C_{IN}/C_{PAH} decrease to their adult values.

The interpretation given here differs from those offered by West *et al.* and Rubin *et al.* in that emphasis has been placed on the probability of a low extraction ratio. If the extraction ratio in infancy proves to be normal, reinterpretation will certainly be required.

In view of the fact that the medulla and juxtamedullary circulation develop ahead of the outer cortical nephrons, one may anticipate that much of the neonatal atubular circulation is through

the *vasa recta*, along the lines described by Trueta and his colleagues[2053] in the adult rabbit kidney. Replacement of these atubular circuits by circuits promoting tubular clearance of all postglomerular blood might occur to a variable extent during maturation in different species. And if the primordial juxtamedullary glomeruli receive a meager sympathetic innervation, it would perhaps explain their resistance, relative to the glomeruli in the neogenic zone, to vasoconstriction. This neuromotor imbalance, so striking in some rabbits, might also represent a fetal pattern which is largely if variably lost in the adults of other species,* explaining the fact that evidence is lacking for the operation of the Trueta by-pass in man (ch. xxv).

This interpretation must await confirmation by the determination of extraction ratios in the infant kidney, and perhaps studies on the distribution of the postglomerular blood in newborn animals.

One difficulty is presented in this view, in that Galán, Peréz-Stable, Martin, and Faéz[735] report that, in 6 children 2 to 11 years old, Tm_G averaged 543 ± 129 (322 to 759) mg., values much greater than those observed in adults (375 ± 79.7 in males and 303 ± 55.3 in females).[1931, 1939] The average Tm_G/C_{IN} ratio in children, 4.35 ± 1.19, is correspondingly greater than in adults (males 2.7 and females 2.5), and is even larger in children with nephrosis.[733] In 2 normal children in whom both Tm_G and Tm_D were determined, the ratio Tm_G/Tm_D averaged 13.0 as compared with 7.32 ± 1.51 in adult males and 8.29 ± 2.09 in adult females. These figures would indicate that glucose reabsorptive capacity is much more highly developed, relative to glomerular function and the excretion of diodrast and PAH, in children than in adults. This circumstance would seem to require, by the foregoing interpretation, extraordinary if transitorily enhanced glucose reabsorptive capacity in all available nephrons. However, in premature and newborn babies, Tudvad[2084] reports that Tm_G corrected to 1.73 sq. m. is below the adult value. The C_{IN}/Tm_G ratio averaged 0.47 (0.34 to 0.66) as compared with 0.395 in adults, confirming a relatively low Tm_G value. Some uncertainty must, therefore, remain attached for the time being to glomerular-tubular balance with respect to glucose reabsorption.

* It may be repeated that, in respect to vasomotor reactivity, the rabbit appears to be a very unstable creature.

MAINTENANCE OF SALT AND WATER BALANCE IN INFANCY

Although presumably in salt and water balance *at birth (if the* mother is in a state of health—the effects upon the infant of salt and water imbalance in the mother have never been examined), the newborn baby is precipitated toward dehydration by the lapse of some 24 to 48 hr. before it imbibes fluid.[2069] The relatively large surface area of the infant favors extrarenal water loss, although Heller [958] has found that such loss is smaller than was expected in newborn rats at room temperature, perhaps because they are poikilothermous, and evaporation is reduced as the body temperature falls. The practice of giving newborn infants water is not universal, even when they are to be reared from a bottle, and abstinence from fluid for 48 hr. would produce significant dehydration in the adult. The first 3 or 4 postnatal days are attended *by loss of 6 to 10 per cent in body weight, which is perhaps chiefly* attributable to dehydration, and from birth until the third day the plasma concentrations of urea, uric acid, and NPN generally increase. For these reasons, McCance [1296, 1305] concludes that, as a rule, babies do suffer dehydration from the fourth until the thirty-sixth hour of life.

Despite neonatal dehydration,[28] as judged by red cell count, hematocrit, and body weight, the plasma sodium concentration and total base are fairly well maintained; urea and potassium concentrations are, however, elevated in newborn infants and newborn rats; [959, 1307] the bicarbonate concentration is reduced below adult mean values by the presence of organic acids, among which pyruvic acid is important, while respiratory compensation maintains the hydrogen ion concentration at pH 7.4. *Incipient* acidosis is easily aggravated, as for example by a shift from breast milk to more acid cow's milk or by diarrhea, or readily relieved and even excessively compensated *into alkalosis by the administration of bicarbonate.*[1296, 1914]

In adults taking their full complement of fluid, the osmotic *U/P ratio in urine collected during the day* will range from 3 to 4, and the specific gravity from 1.015 to 1.025. During hydropenia, the urine flow is rarely less than 500 cc , this figure depending to a *considerable* extent upon the salt and protein intake, and the

osmotic U/P ratio increases to its maximal value of 4.0 to 4.2, t specific gravity to 1.028 or higher

Heller[959] has shown that adult rats, when deprived of water, excret a concentrated urine (specific gravity 1.056 ± 0.002, 2.0 osm or more) whereas in newborn rats dehydration does not increase the specific gravity (1.011 to 1.015) of the urine significantly, this failure to effect concentration being reflected in failure of the U/P ratios of sodium, chloride, and potassium to increase. Where adult rats increase potassium excretion during dehydration, newborn rats excrete less potassium. Adult animals maintained their extracellular fluid by increasing tubular water reabsorption and by a shift of water from the intracellular space; such water conservation as was effected by newborn rats, which may be the result of a decrease in filtration rate, was inadequate to prevent hemoconcentration and elevation of plasma urea.

According to Thomson,[2069] full-term infants excrete some 20 cc. of water per day in the first 2 days, this figure rising to 225 cc. by the twelfth day. These figures would correspond to about 100 and 1125 cc. per 1.73 sq. m/day The specific gravity in the first 2 days has a wide range (1.008 to 1.020) with a mean of 1.012, it decreases thereafter for several weeks and levels off in the range 1.006 to 1.011, with a mean of 1.008 During the first 48 hr. after birth, the urine is slightly more concentrated than the plasma, the osmotic U/P ratio ranging from 1.0 to 1.4,* then, from the third day on, the urine becomes more dilute, the osmotic U/P ratio falling to 0.3 to 0.7, this decrease in osmotic pressure being only in part related to fluid ingestion, which is now established at 300 to 500 cc/day.[955, 1307] The urine remains dilute for at least a week, when the kidney begins to do better osmotic work.[955, 1307, 2282] At 1 month, the specific gravity during water deprivation may rise to 1.036 and the osmotic concentration to 1.2 osm/liter (osmotic U/P ratio about 3.6), figures comparable to those of adults, and by this time over half the water provided by the infant's usual food can be conserved to cover abnormal losses by other routes of water removal.[1458]

*The reason for this limitation in osmotic pressure is obscure, for Dean and McCance[465] have shown that at least 2 infants 3 and 4 days old concentrated to an osmotic U/P ratio of 1.5 to 2.0 during hypertonic saline diuresis, and in 1 this value reached 2.5 during urea diuresis. However, these figures are still less than are observed in adults

Thus the kidney of the newborn is unable to make a significantly concentrated urine during the critical period of dehydration immediately after birth. But, as McCance and his coworkers have emphasized, the urine volume remains low, presumably because a low filtration rate reduces the load of sodium chloride and other solutes escaping reabsorption.

The deficiency in concentrating power in infancy is attributed by Heller to relative insensitivity of the distal tubules to ADH, for the concentration of the urine was but slightly affected by the administration of pitressin to full-term infants 2 to 6 days old who were excreting relatively dilute urine. He correlates this lack of sensitivity with the fact that the neurohypophysis of young animals contains relatively little of this hormone.[955, 957] Assay of the pituitary gland in 15 newborn infants revealed only about one-fifth of the antidiuretic and oxytocic hormones per mg. of dry tissue found in the glands of 14 adults. However, Barnett *et al.*[93] obtained inulin U/P ratios as high as 227 in premature infants who were moderately dehydrated, and they suggest that measurements of osmotic pressure and specific gravity are misleading in this connection, since they depend not only on water reabsorption but on the reabsorption of urinary solutes. These investigators found that a 6-day-old, 2200 gm. premature infant deprived of water for 16 hr. showed an inulin U/P ratio of 200; after the intravenous administration of 0.9 per cent saline the U/P ratio fell to 20 and below; immediately after the infusion of pitressin at 1 milliunit/min. the U/P ratio rose to about 60. The experiment indicates some responsiveness on the part of the tubules to ADH.* The distal tubules may appear to be less sensitive to ADH in respect to water reabsorption because the maximal osmotic ceiling may be low, thus placing a low limit upon the degree of concentration of the urine even under maximal ADH activation.

The fact that infants under 3 months of age respond poorly to water diuresis,[1295] a phenomenon also observed in puppies[29] and newborn rats,[958, 1306] is probably related to the low filtration rate

* The use of saline instead of water to hydrate the infant may have produced osmotic diuresis, and one could not expect to obtain as high a U/P ratio with pitressin alone, which may have promoted the excretion of sodium chloride, as on water deprivation with a low load of urinary solutes.

and the delivery to the distal system of a correspondingly small load of sodium and water. In rats, typical water diuresis begins to appear at 4 days, and at 12 days the response is almost indistinguishable from that of the adult, despite the fact that during oliguria the urine remains relatively dilute.[1306] The situation recalls the blunting of water diuresis in Addison's disease (p. 353).

Sodium, chloride, and potassium clearances are relatively low in newborn full-term infants, on the basis of surface area possibly only one-fifth of those of adults. These low clearances also appear to be related to the low filtration rate. At all ages, the chloride clearances tend to vary with the urine flow, which is to be expected if the urine is (for the infant kidney) maximally concentrated and sodium chloride is the chief deterrent to water reabsorption. The phosphate clearance is also low and tends to vary with the urine flow.[1407, 2283 2284] Young, Hallum, and McCance[2282] have emphasized the potential importance of the low filtration rate, with resulting glomerular-tubular imbalance, in the genesis of low electrolyte clearances, and, in turn, the importance of low electrolyte clearances in the susceptibility of premature and full-term infants to the formation of edema. The situation can be illustrated by the calculation that, if one takes the average filtration rate in the newborn as 50 cc/min. per 1.73 sq. m., and the adult figure as 130 cc., and if one allows for the lower concentrating power (one-third) in the infant kidney, the expected *urine obligatoire* in infants would be of the order of 800 cc/day per 1.73 sq m. *That the observed urine flow is lower (300 cc or less) may* be referable, as McCance[1296] suggests, to the fact that the low filtration rate reduces the load of solutes delivered to the distal tubule.

Isotonic and hypertonic saline are poorly excreted by young animals. When 10 per cent sodium chloride or 20 per cent urea solutions are administered by mouth to adult rats in doses of 5 per cent of the body weight, the animals respond with a diuresis which enables them to excrete 27 per cent of the solute in 5 hr. As in man, the urine during this diuresis becomes relatively dilute, dropping from the range of 2.5 to 3.0 osm. to 1.3 to 1.5. In newborn rats, however, the maximal control concentration is rel-

atively lower (0.5 osm.), and hypertonic saline and urea solutions produce only a slight diuresis, with a slight increase or no change in osmotic pressure.[1306] Newborn infants respond to osmotic diuresis in a similar manner: diuresis is substantially less than in the adult and the osmotic pressure of the relatively dilute urine rises slightly or does not change.[482, 485] This inability of the infant to dispose of hypertonic or even isotonic solutions of sodium chloride would appear to issue in the first instance, as McCance and his coworkers emphasize, from glomerular-tubular imbalance, and in the second instance, assuming excretion into the urine, from the inability of the infant kidney to elaborate a hypertonic urine. The infant is faced with a dual danger: first it is handicapped in excreting sodium chloride, and, if the salt is excreted, it is apt to suffer dehydration by excessive loss of water. Sluggishness in excreting saline does not appear to issue from failure of the glomeruli to increase their activity on expansion of the body fluids, for Dean and McCance[486] found that 0.91 gm/kg. of sodium chloride as a 10 per cent solution markedly increased the filtration rate in 2 infants 3 and 4 days old, though the maximal rate attained (20 cc/min. per 1.73 sq. m.) fell far short of the adult value.*

Infants may remain in a state of acidosis for some time after birth. The phosphate clearance is so low[484] that there is available very little substrate buffer for the excretion of acid, and as a result a larger proportion of acid is neutralized by ammonia than in adults. The proportion of free acid as phosphate is also much lower and the proportion as organic acid much higher.[1298]

Dean and McCance[483] obtained exogenous creatinine/inulin clearance ratios ranging from 0.68 to 1.32, and averaging about 1.0, in infants a few days old (the ratio tended to increase in successive periods),† and inferred that the tubular excretion of creatinine is not fully developed. Brod and Sirota[264] report that in somewhat older infants the endogenous chromogen/mannitol clearance ratio averages 0.60 ± 0.066 (0.55 to 0.69), whereas this ratio

* It should be emphasized that adult humans respond very sluggishly to the administration of isotonic saline in comparison with the dog (ch. XI) and possibly the rat, and it may be that part of the trouble with the infant kidney is that it is human.

† This may reflect poor perfusion of some tubules, as is suggested in connection with pyelonephritis (ch. XXVI).

averages 1.0 in normal adults[262] In 15 older children, the creatinine/inulin clearance ratio averaged 1.13.[1593]

Barnett and his coworkers[93] conclude that there is no significant back diffusion of inulin in the renal tubules of premature infants, because a constant clearance of inulin may be maintained in the presence of wide variations in water reabsorption and the mannitol/inulin clearance ratio is the same (0.883 ± 0.07) as in adults (0.90 ± 0.07).

The limitations of the infant kidney present a liability that can only be offset by judicious restraint in the administration of salt, of saline infusions, and of a high protein diet. Human milk is low in salt, and the relative proportion of protein and fat are such that a large fraction of the total calories are supplied by the latter, thus conserving water from the requirement of urea excretion Conversely, the kidney cannot do much to compensate for increased water loss in fever, vomiting, or diarrhea. Against any factor tending to expand or contract the body fluids, the infant has but a narrow margin of renal functional defense.

CHAPTER XVII

Comparative Physiology of the Kidney

TELEOSTOMI (BONY FISHES)

From the data of paleontology and comparative anatomy it has been propounded [1390, 1406, 1923, 1924, 1926, 1931] that the protovertebrates were evolved in the fresh-water rivers of the Cambrian or Ordovician Period, and that the glomerulus represents an adaptation added to the primitive nephrostomatous tubule permitting the excretion of large quantities of water at the expense of energy supplied by the heart. All those fishes which have had a continuous fresh-water history retain well-developed glomeruli; through the Devonian air-breathing fishes (Crossopterygii) the glomerular kidney was transmitted to the Amphibia and their descendants, the reptiles, birds, and mammals. With the exception of the Elasmobranchii, *those fishes which one time or another have invaded* the sea and made it their permanent home have reversed the environmental osmotic gradient, the higher osmotic pressure of sea water tending to draw water from the body through the gills, oral membranes, and skin. The capacity to elaborate a hypertonic urine was not developed until the evolution of the birds and mammals, and in the marine fishes the urine is isotonic with the blood. Apart from a very limited quantity of water formed by metabolism, they must replace any water lost through the skin and gills and obtain additional water for urine formation from the sea. They do this by drinking sea water, absorbing the sodium chloride and water (magnesium and sulphate are poorly absorbed) from the gut, and excreting the sodium chloride through the

gills, leaving osmotically free water in the body. This circuitous process requires that practically all the sodium in the ingested sea water be excreted by the gills against an osmotic pressure gradient represented by the difference between that of the blood ($\Delta = -0.6$ to $0.8°$ C.) and of sea water itself ($\Delta = -1.86°$ C.), a process which requires a considerable expenditure of energy for each liter of urine formed.* Consequently, where in fresh-water fishes the urine flow is abundant and the filtration rate relatively high, in marine fishes the urine flow is minimal and the filtration rate correspondingly reduced. No longer an advantageous adaptation, the glomeruli in the marine fishes have undergone marked reduction in size and capillarity, and in many forms have disappeared entirely, leading to the formation of the aglomerular kidney. In the daddy sculpin (*Myoxocephalus scorpius*) the glomeruli degenerate during the life of the individual and large (and old) fishes are sometimes entirely aglomerular, excreting no trace of ferrocyanide or inulin (Forster, pers. com.).[839]

The few data available on fresh-water fishes indicate urine flows of 200 to 400 cc/day per kg.[1919, 1923] It is probable that there is little tubular reabsorption of water, and that the filtration rate is correspondingly high. Burgess, Harvey, and Marshall[294] have shown that in the fresh-water catfish (*Ameiurus nebulosus*) ADH has no effect on the rate of urine excretion.

In the marine fishes the urine flow is quite low (2 to 5 cc/day per kg.) and the filtration rate correspondingly reduced. Variations in urine flow are related to and probably regulated by variations in filtration rate.

For reasons not clear, when marine teleosts are kept overly long in captivity and traumatized by nets, live-cars, etc., they develop marked diuresis, with a corresponding increase in filtration rate.[837, 1623] Chloride, normally absent from the urine, is now excreted in increasing amounts along with large quantities of magnesium and sulphate, indicating that the diuresis is a result of increased ingestion of sea water. The sequence of events seems to reflect a breakdown of the defense of the organism against environmental dehydration, or what Graffin called 'osmotic

* The nature of the cells that [illegible] subject of debate. The writer ag[illegible] spiratory epithelium of the gill [illegible] while Keys and Willmer[1114] and [illegible] function to special cells resembling mucous cells. Copeland, however, suggests that these 'chloride' cells are probably concerned only with anion transfer; if such is the case, the transfer of base (chiefly sodium) from blood to sea water must be attributed to the general respiratory epithelium, though how base could be transferred without anion is not clear.

strain.' It is of some interest that normally the urine may be supersaturated with $MgHPO_4 \cdot 3H_2O$, which crystallizes massively on withdrawing the urine from the bladder.[1623]

Clarke[398] found that the xylose * U/P ratio in the sculpin, *Myoxocephalus octodecimspinosus*, tends to remain constant at about 4.0 with progressive diuresis until the urine flow reaches relatively high values, when the U/P ratio falls toward or to 1.0. The normal filtration rate is of the order of magnitude of 14 cc/day per kg., the urine flow about 3 cc. Under conditions of osmotic strain the filtration rate increases to 100 cc/day per kg. It appears that glomerular activity is physiologically reduced in the sculpin by some inhibitory mechanism to a level considerably below the maximum. This may involve intermittent glomerular activity, as in the frog.

ELASMOBRANCHII (SHARKS, RAYS, SKATES, AND CHIMERAE)

The elasmobranch fishes took up life in salt water earlier than and independently of the invasion of the sea by the bony fishes. Although many elasmobranchs reinvade and breed in fresh water (the Chimerae are an exception), the Sub-order appears to have had a continuous marine history from the time of its evolution. As noted in the discussion of the excretion of urea (p. 79), this substance is actively reabsorbed by the renal tubules in all the elasmobranchs, and the concentration in the blood is thereby raised to some 2000 to 2500 mg/100 cc. This 'physiological uremia' increases the osmotic pressure of the blood to a point where small quantities of water can be absorbed osmotically from sea water through the gills and oral membranes, and thus liberates the organism from the task of separating water from sea water by oral ingestion.[1926 1931] The glomeruli are large and well developed. Glomerular function is no disadvantage to the elasmobranchs and there is no evidence of glomerular degeneration among them, as in the marine teleosts.

The data on the control of glomerular activity in the marine elasmobranch fishes are meager, but they indicate that the rate of filtration and the urine flow are relatively large and constant (*c.*80 and 20 cc/day per kg, respectively). There appears to be no inhibition of renal activity in the normal animal, and as collapse occurs in 'sick fish' the filtration rate progressively decreases. It may be that, because of their physiological uremia and superior osmotic position, they have never been faced with the necessity for evolving mechanisms for reducing glomerular activity.[1406]

* Clarke[397] subsequently showed that the xylose/inulin clearance ratio in the sculpin averaged 0.81 (0.70 to 0.95).

Clarke[390] found that theophylline and salyrgan do not produce diuresis in the dogfish. Phlorizin produces moderate diuresis, probably in consequence of the osmotic activity of the glucose in the urine. Adrenalin in large doses induces diuresis and blocks the tubular reabsorption of urea, causing in 1 experiment a 55-fold increase in the urea clearance and a change in urine flow from 16 to 75 cc/day per kg.

Dogfish transferred from undiluted to diluted sea water (70 per cent) showed a progressive increase in urine flow; the U/P ratio of inulin remained remarkably constant, the inulin clearance rising in proportion to the urine flow. One fish, which in sea water had a filtration rate of 90 cc. and a urine flow of 20 cc/day per kg, showed in the second 12 hr. period in 70 per cent sea water a filtration rate of 272 cc. and a urine flow of 61 cc[330]

In the fresh-water sawfish, *Pristis microdon*, which is identical with the marine species, the urine flow ranges from 150 to 460 (average 250) cc/day per kg.[1926] The filtration rate is unknown, but it is clear that glomerular activity and the filtration of water increase under conditions of hydration

AMPHIBIA

The Amphibia have had a continuous fresh-water history since their evolution in the Devonian-Carboniferous periods No marine amphibian, and none living under arid terrestrial conditions, is known, and extant forms, even the land toads, cannot survive water deprivation for long. The glomeruli are large and the capillary tree elaborate and free of invasive tissue Again, the antidiuretic hormone has no effect on the reabsorption of water by the tubules,[394] and variations in urine flow are mediated almost entirely by variations in the filtration rate.

Forster[874] has shown that in the bullfrog, *Rana catesbiana*, the urine flow is almost a linear function of the filtration rate: the average filtration rate at a urine flow of 1 cc/hr per kg is 3 5 cc/hr per kg., rising to an average of 20 * at a urine flow of 15 By following glucose Tm, Forster[874] demonstrated that the increase in filtration rate involves the recruitment of inactive glomeruli, conforming with the classical observations of Richards and Schmidt[1114] that the glomeruli in the frog are not all active and that glomerular activity can be increased by expansion of blood volume and other means (injection of urea, glucose, sodium sulphate, caffeine, small doses of pituitrin, and section of the sympathetic nerves), and reduced by adrenalin, large doses of pituitrin, or

* These figures were obtained in fall and winter frogs There appears to be a seasonal variation, for in spring frogs Forster[877] reports filtration rates up to 50 cc/hr per kg

stimulation of the vasoconstrictor nerves, observations which have been repeatedly confirmed by others.[28, 156, 593, 1709, 2186, 2187] Bieter[156] has described a short capillary loop in the common frog (*Rana pipiens*) which acts as a shunt, permitting blood to flow across the glomerulus without extensive exposure in the longer capillaries. Forster[677] finds that in the bullfrog with the renal-portal circulation intact the filtration fraction is 6 per cent, when the renal-portal circulation is excluded, this figure is 12 to 15 per cent. The diodrast clearance with the renal-portal circulation intact averages 700 cc., without the renal-portal circulation, 350 cc/hr. per kg.

REPTILES

The reptiles were evolved from an amphibian stock in the arid Pennsylvanian-Permian periods which followed the Carboniferous. They are adapted to living away from water and most of them can survive considerable periods of aridity. Burgess, Harvey, and Marshall[294] found *that pitressin in small doses markedly reduces the filtration rate (xylose* clearance) but obtained no indication that it increases water reabsorption by the tubules.

Friedlich, Holman, and Forster[698] have shown that in the fresh-water turtle, *Psuedemys elegans*, the filtration rate varies with the urine flow. There is no tubular excretion of creatinine, but xylose is reabsorbed to the extent of about 10 per cent. High endogenous glucose plasma levels are attained during experimental manipulation, and lead to glucosuria. *After phlorizination, the reabsorption of glucose is blocked but the per*meability of the tubules is increased, permitting the reabsorption of glucose, xylose, and creatinine (relative to inulin) to the extent of about 15 per cent.

Marshall[1394] found that in phlorizinized iguanas (*Iguana iguana*) the glucose U/P ratio averaged 3.2 and the uric acid U/P ratio 51.4, demonstrating the tubular excretion of the latter. (In the phlorizinized chicken these ratios averaged 12 and 136.4.)

Urea is absent from the blood and urine of the alligator (*Alligator mississipiensis*), the chief non-protein nitrogenous constituents of both being ammonia, which has an average concentration in whole blood of 61 mg/100 cc. The urine is invariably alkaline (pH 7.18 *to* 8.02) *and* rich in bicarbonate (77.6 to 125 mEq/liter), and in fasting animals contains no more than a trace of chloride and very little sodium.[437]

Shannon (pers. com.) obtained inulin U/P ratios of 5.44 to 11.37 (most of them between 5.0 and 7.0) in this species at urine flows of 0.005 *to* 0.087 *cc/min.* (3 kg. *animal*). It is apparent that changes in hydration

are accompanied by changes in filtration rate, as in other cold-blooded animals.

CHICKEN

In the birds, evolved from a primitive reptilian stock, the thin limb of the loop of Henle first makes its appearance in some but not all nephrons, and for the first time the antidiuretic hormone accelerates the tubular reabsorption of water, though large doses (0.5 unit/kg.) also reduce the filtration rate, as in the alligator, though not to the same extent.[294]

Glomerular development is, however, poor. The glomeruli are small and heavily invaded by inert tissue, the glomerular tuft sometimes being reduced to a few short capillaries. No aglomerular bird is known, but even the chicken is not far from that state. Functional study of the marine birds, which subsist for long periods (up to 9 months) in the open sea without access to fresh water, might reveal that glomerular function has diminished to close to zero. This degeneration of glomeruli is undoubtedly related to the uric acid habitus which is so strikingly developed among this Class and the arid-living reptiles (ch. v).

In the chicken, the massed data of Pitts [1678] and Shannon [1868] show only a slight upward drift of the inulin clearance with urine flows from 0.4 to 1.8 cc/min. But, as Korr [1161] points out, these observations were made after the peak and on the descending limb of water diuresis. Korr believes that during optimal hydration the filtration rate averages about 1.22 cc/min. per kg., this figure dropping to 0.60 cc. during dehydration and rising to 2.19 cc. through the postdiuretic period. But apparently variable reabsorption of water under the influence of ADH is important in diuresis, as in the mammals.

Lambert [1194] obtained an average inulin clearance of 1.71 cc/min. per kg. He has confirmed the excretion of creatinine by the tubules in the chicken, demonstrated the excretion of uroselectan B (iopax), and showed that the administration of uroselectan B depresses the creatinine/inulin clearance ratio. Lambert also finds that the filtration rate is decreased in vitamin B deficiency.

DESERT MAMMALS

So far as is known, most desert mammals cannot withstand dehydration much better than can man, the outstanding difference consisting of a better ability to conserve water.[207, 820, 2128, 2121] To this group belong the antelopes, camel, donkey, and several other herbivores. The rodents, like the desert reptiles and insects, seek cool places during the hot hours of the day instead of using their water for heat regulation. Notable

among the rodents are the kangaroo rats, *Dipodomys merriami* and *D spectabilis*, and Bailey's pocket mouse, *Perognathus baileyi*, studied by Howell and Gersh [1043] and by Schmidt-Nielsen and his colleagues.[1788, 1790, 1791, 1792] These rodents normally live on air-dried seeds and can survive for long periods and gain weight on a diet of dry grain or oatmeal which contains only 5 to 10 per cent free water and affords about 0.6 cc. of water for each gm of carbohydrate oxidized. Temperatures above 35° C. are quickly fatal, but in the burrows a foot or so underground the daytime temperature never exceeds 35° C., and averages about 28° C. These animals have to be taught to drink free water, and while some of them will eat succulent food, *P. baileyi* disdains it and will not eat fresh watermelon. There is no water-storage mechanism in the body, but the kidney elaborates a remarkably concentrated urine In *Dipodomys merriami* the electrolytes, as measured by electrical conductivity, may reach 914 mEq (not chloride, for there is a very low chloride intake), which, as sodium chloride, would have a freezing point of −2.8° C.* and a simultaneous urea concentration of 14 per cent (Δ = c.4.22° C.). The average urine figures in *D spectabilis* are 702 mEq. of electrolyte (Δ = c.2.2) and 7.8 per cent urea (Δ = 3.4° C.), and in *P. baileyi* (disdaining fresh watermelon in preference to dry grain), 923 mEq of electrolyte (Δ = c.2.7° C.) and 12 per cent urea (Δ = 3.66° C.). Howell and Gersh [1043] report a sample of *D. mohavensis* urine with a urea content of 19.7 per cent These authors suggest that the collecting tubules play an important role in the reabsorption of water in this species. Schmidt-Nielsen *et al.*[1791] report that the highest urea figure in their data (22.1 per cent) occurred simultaneously with the highest electrolyte concentration (1180 mEq); the writer estimates the osmotic pressure of this urine to be 5.68 osmolar (Δ = −10.4° C.), which would give an osmotic U/P ratio of about 17, as compared with a maximal ratio of 4.2 in man. Under the same dietary conditions the white rat (*Rattus narvegicus var. alb.*) loses 52 per cent of its body weight and dies in 15 to 21 days, apparently chiefly because it cannot concentrate the urine to the same degree. The desert rodents cannot endure a high protein diet (pure soy bean), presumably because of the low water/urea ratio in metabolism [1791]

When fed barley dried at 105° C. and containing about 10 per cent sodium chloride, *P. baileyi* survived only 2 to 17 (average 7) days. On the second day on this diet the urine had an electrolyte content of 1220

* In calculating Δ, we take the activity coefficient of NaCl as 1.7, not as 2.0 as Schmidt-Nielsen *et al.* do. Even our estimate is probably high for so concentrated a solution.

mEq (908 mEq. of chloride) and a urea content of 12.5 per cent. The first figure is the highest concentration of electrolyte recorded in the urine of any animal, and is more than twice as concentrated as sea water (585 mEq.). (Adolph[30] gives the maximal concentration of chloride as 600 mEq. for the white rat, 370 mEq. for man, 330 mEq. for the dog, and 320 mEq. for the goat.) *D. merriami* can survive on a diet with a sodium content far below the minimum required by the domestic albino rat, and can survive slightly longer on a diet containing excessive amounts of sodium or potassium. Under both conditions the albino rat shows marked renal injury[1124] *D. merriami*, ordinarily with no taste for water, will take fluid if fed on a high protein diet (soy beans), under which condition it passes into negative water balance because of the large quantity of urea requiring excretion. On such a diet it will drink even sea water, and, at least over a period of a few weeks, does just as well as when drinking fresh water, with no change in plasma concentration of total electrolytes.

MARINE MAMMALS

The marine mammals are, of course, all descendants of terrestrial, fresh-water drinking forms, and it was necessary that adaptation liberate them from dependency on fresh water before the sea could become their permanent habitat.*

Irving, Fisher, and McIntosh[1081] inferred from chloride analyses of urine and fecal material removed from young anesthetized seals that these animals did not drink sea water, water for urine formation being derived from the food. They estimate that out of the 1000 gm. of water made available by 1250 gm of herring (1000 calories), 200 gm. would be required for evaporation from the lungs and for feces. The remaining 800 cc. would be available for renal excretion.

Smith[1977] showed that the rate of urine formation in the fasting harbor seal, *Phoca vitulina*, is normally low, ranging from 0.06 to 0.1 cc/min. in a 40 lb. animal After a meal of herring the rate increased to a maximum of 1 cc/min, maximal diuresis being reached 4 to 7 hr after the meal, the urine flow thereafter decreasing to low levels again. Thus urine excretion increases as water becomes available from the ingested food and falls again to oliguric levels during fasting. Urea is the predom-

* The Eskimos are aware that seals do not drink fresh water, and they con- [illegible]

ful a hunter

inant nitrogenous substance, along with ammonia, creatinine, and creatine (apparently of exogenous origin). From the composition of the urine and rectal contents it was concluded that the animal does not ingest sea water while fasting, and that no more than traces of sea water are taken in with the food. A seal will frequently swallow large herring under water; apparently the esophagus closes firmly about the morsel of food and any sea water present in the mouth or taken into the esophagus is ejected backward into the oral cavity.

The composition of the urine is in no way remarkable except for the degree of osmotic concentration. The quantity of sulphate in the urine is not excessive (less than 1.85 mM/gm. of nitrogen), the chloride content is that to be expected on a fish diet, and only small quantities of magnesium are excreted. The osmotic pressure ranges from $\Delta = -1.365$ to $-3.988°$ C., the lowest values being observed in the fasting, oliguric state when energy is supplied largely by the oxidation of carbohydrate and fat and when the loads of urea and sodium chloride claiming excretion are minimal. The maximal osmotic pressure does not coincide with the maximal rate of urine formation but at intermediate values of the latter, indicating that it is not solely the osmotic load in the urine that determines the rate of urine formation. The highest osmotic pressure recorded represents an osmotic U/P gradient of about 5.7, as compared with 17 in the kangaroo rat and 4.2 in man.

It seems probable that the evidence on the seal can be generalized to include all marine mammals. Even in the whalebone Cetacea, which subsist upon plankton, the urine is no more concentrated than in the seal. The 'comb' of the whalebone whales is adapted to filter microscopic organisms out of the water in such a manner that the material deposited can be licked off by the tongue, which probably 'dries' it by compressing it into a compact bolus before deglutition.

Fetcher [639] subsequently arrived at the conclusion that the seal does not drink sea water from analyses of the total solid content of the urine, but he believed that the conclusion could not be extended to the whalebone whale and other mammals that live on invertebrates. No evidence that such mammals do drink sea water is given, however. Fetcher and Fetcher [640] have shown that the dolphin absorbs more salt than water after the oral administration of 0.5 M sodium chloride.

Hiatt and Hiatt [935] have shown that the postprandial diuresis in the seal is accompanied by a marked increase in the filtration rate, this value increasing from 0.2 cc/min. per gm. of kidney during fasting to 1 cc/min. after a meal of herring, maximal renal function being reached in a few hours. The filtration fraction tends to remain constant, and Tmg does

not decrease during fasting oliguria, indicating that the decrease in renal function is not attributable to complete cessation of activity in some glomeruli,* but is shared fairly uniformly by all glomeruli. Hiatt and Hiatt concluded that the effective stimulus to the increased filtration rate and renal blood flow in the fed animal is not available water but probably is associated with the metabolism of the ingested protein.

Irving and his collaborators [1063] have shown that the seal, like other diving mammals, can survive considerable periods of asphyxia during diving by a co-ordinated mechanism which involves respiratory inhibition and maintenance of arterial blood pressure despite marked vagal bradycardia. It is demonstrated in the beaver that during this asphyxial reflex the blood flow to the muscles is decreased and that to the brain increased. Bradley and Bing [233] found that the asphyxial reflex in the seal can be elicited by submerging the animal's head under water, or more simply by holding the nostrils closed with a towel or funnel. They have demonstrated that, during the asphyxial reflex, the filtration rate and renal plasma flow are markedly decreased, the filtration fraction remaining nearly constant. A considerable quantity of blood is thus diverted from the kidneys and made available for circulation to the brain or elsewhere Atropine blocks the reflex bradycardia but does not block the renal ischemia. Bradley and Bing have shown that, as in man and the dog, pyrogenic inulin produces renal hyperemia, increasing the renal plasma flow from the average control value of 1 03 cc/min per gm. KW to 3 27 The hyperemic phase is preceded by a marked vasoconstrictor phase A single dose of amidopyrine (1 3 gm.) blocked the febrile reaction without blocking the renal hyperemia with moderate doses of pyrogen, but with larger doses of pyrogen the body temperature rose to 107° F and the animal died within an hour.

RAT †

The development of a technique for the collection of blood and urine in the rat has presented numerous difficulties. All investigators have used a single urine collection period Some have used a terminal blood sample from single animals or pooled samples obtained from several animals, while others have drawn tail blood in the middle of the urine

* This also excludes a non-glucose reabsorbing shunt.

† The writer does not have much more confidence in the white rat as an experimental animal for comparison with man than he does in the rabbit. It should be noted that the Wistar strain, for example, comes from the King A albino strain established by Helen Dean King at the Wistar Institute in 1904, and has been bred successively for 139 generations. Although in recent years it has been cross-bred rather than inbred, the net biological effect of selection

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TABLE X

Renal Clearance Data in Rats

(All values are expressed per 100 gm body weight.)

Filtration rate cc/min.	Effective plasma flow cc/min.	Filtration fraction	Tm_{PAH} mg/min.	Tm_{D} mg iodine per min.	Authors
0 27 ± 0 06	1 33	0 20		0 142	Friedman, S. M., *et al.*[714]
0 35	2 02	0 17		0.126	Dicker *et al.*[414]
0 347 ± 0 043	2 22 ± 0 28	0 17 ± 0 037		0 132 ± 0 0185	Dicker *et al.*[416]
0 60 ± 0 031	2 66	0 23		0 183 ± 0 0135	Braun-Mendenez *et al.*[187]
0 66 ± 0 028	2 50	0 24			Friedman, M[708]
0.65 ± 0 019	4 14	0 16	0 18 ± 0 005		Friedman, S M., *et al.*[720]
0.915 *†	2 63				Lippman[1164]
1 49 *‡	3 38				
0.55 ± 0 085 ‡			0 327 ± 0 016		Corcoran *et al.*[419]
0 61 ± 0 016 *			0 29 ± 0 0056		Corcoran *et al.*[416]
0 43 §					Dicker[413]
0 76 ‖					
0 73 *					Lotspeich[1274]
0 82 *					Boss *et al.*[224]
0 58	1 89	0 31		0 117	Watschinger *et al.*[2111]

* Creatinine
† 'Tail cutting' method
‡ 'Undisturbed' method
§ 18 per cent casein diet
‖ 25 per cent casein diet

collection period, or at the beginning and at the end. Some have used whole blood and some have used plasma. Some have ligated the penis, some have catheterized the bladder and some have expressed the urine with pressure. The use of terminal blood is open to the obvious errors of extrapolation, particularly with diodrast and PAH, while the collection of blood before or during the clearance period runs the risk of reflex excitation of the renal vasoconstrictor paths. In addition to technical difficulties, Dicker[810, 813] has shown that below a certain minimal protein intake in the diet (which itself influences the filtration rate, as in the dog) the inulin clearance increases with urine flow. (In these determinations Dicker used the intramuscular injection of inulin and terminal blood samples.)

The results obtained by various investigators have been summarized in table x. S M Friedman and Livingstone[718] administered diodrast subcutaneously in 4 cc. of 2 per cent sodium sulphate solution, inulin subcutaneously in saline. No water was given orally; the penis was ligated and urine expelled by pressure and a midperiod blood was drawn under ether anesthesia In the calculation of Tm_D, FW was taken as 0.62. The authors give the derived data $C_D/Tm_D = 9\,3$, $C_{IN}/C_D = 0.20$. C_{IN} and C_D were independent of urine flow.

Dicker and Heller[814] administered diodrast and inulin subcutaneously in saline, and gave 50 cc/kg. of water orally; urine was expelled by pressure and a terminal blood sample was used. The inulin clearance was constant at plasma inulin levels ranging from 5 to 314 mg/100 cc. of serum, and this and the diodrast clearance were constant at urine flows ranging from 0 0035 to 1 030 cc/min. per 100 gm. BW. The average figures from 104 simultaneous clearances on 35 male rats were: inulin clearance, 0.351 cc, diodrast clearance 2.023 cc, Tm_D 0.126 mg. of iodine per 100 gm. BW. FW was taken as 0.62 after Friedman and Livingstone.

Dicker[810] and Dicker and Heller,[814, 816] using the same technique, report for 134 male rats (mean weight 176.5 gm): inulin clearance 0.347 ± 0.043, diodrast clearance 2 22 ± 0.281 cc., Tm_D 0.132 ± 0.185 mg. of iodine per 100 gm BW, filtration fraction 0.17 ± 0 037.

Braun-Menendez and Chiodi[247] administered inulin and diodrast

within the strain for rapidity of maturation, size of litters, docility, etc., has not been evaluated

Had a sibling pair of *H. sapiens* been selected on a similar basis and inbred or narrowly cross-bred for 139 generations (at 25 years to a generation, from 1525 B C) few students of physiology would expect them to react to stresses in a manner comparable to *H. sapiens* or *Canis familiaris*, both of which are generally represented in physiological investigations by mongrel individuals.

TABLE X

Renal Clearance Data in Rats

(All values are expressed per 100 gm body weight.)

Filtration rate cc/min.	Effective plasma flow cc/min.	Filtration fraction	Tm_{PAH} mg/min.	Tm_D mg. iodine per min	Authors
0.27 ± 0 06	1.33	0 20		0 142	Friedman, S. M., *et al*[718]
0.35	2 02	0 17		0 126	Dicker *et al.*[514]
0 347 ± 0 043	2 22 ± 0 28	0 17 ± 0 037		0 132 ± 0 0185	Dicker *et al.*[510]
0 60 ± 0 031	2 66	0 23		0 183 ± 0 0135	Braun-Mendenez *et al*[217]
0.66 ± 0 028	2 50	0 24			Friedman, M.[708]
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1.49 *‡	3 38				
0.55 ± 0.085 ‡			0 327 ± 0 016		Corcoran *et al.*[433]
0.61 ± 0 016 *			0 29 ± 0 0056		Corcoran *et al.*[410]
0 43 §					Dicker[512]
0 76 ‖					
0.73 *					Lotspeich[12 4]
0 82 *					Boss *et al.*[214]
0 58	1 89	0.31		0 117	Watschinger *et al.*[2161]

* Creatinine
† 'Tail cutting' method
‡ 'Undisturbed' method
§ 18 per cent casein diet
‖ 25 per cent casein diet

subcutaneously, the former in 3 cc. of saline, and 50 cc/kg of water orally; urine was expelled by pressure and a terminal blood sample was used No statement is made in regard to FW. The inulin and diodrast clearance and Tm_D are all reported to increase with urine flow: $C_{IN} = 14.81V + 0.0916$ and $C_D = 64.56V + 0.661$, where C_{IN}, C_D and V are expressed as cc/min. per 100 sq. cm Tm_D averaged 0.1016 ± 0.041 mg of iodine per 100 sq. cm. The filtration fraction averaged 0.226 (0.117 to 0 502). C_{IN} as given in table x was recalculated by Corcoran *et al.*[410] and Tm_D was recalculated by the writer.

M Friedman[702] gave creatinine orally in 3 doses of water (10, 5, and 5 cc) at 1 hr. intervals, and inulin and PAH subcutaneously; urine was expelled by pressure and pre- and post-clearance blood samples were collected from the tail under ether anesthesia; whole blood was used for creatinine determination, plasma for inulin, the creatinine data being used without correction. C_{IN} in table x was recalculated by Corcoran *et al.* and C_{PAH} by the writer. C_{CR}, C_{IN}, and C_{PAH} increased with urine flow, but regression equations are not given. At equal urine flows, the creatinine and inulin clearances in separate determinations averaged about the same, while in 41 simultaneous determinations the creatinine/inulin clearance ratio averaged 1 023 (0.72 to 1.73); in 12 simultaneous determinations the inulin/PAH clearance ratio averaged 0.24 (0 19 to 0 39), and in 35 simultaneous determinations the creatinine/PAH clearance ratio averaged 0.22 (0.14 to 0.38). The creatinine clearance was independent of the plasma concentration of creatinine between 1.0 and 26 6 mg/100 cc Friedman concluded that there is no tubular excretion of creatinine in this species.*

S. M. Friedman, Polley and C. L. Friedman[720] gave inulin intraperitoneally in 3 cc of saline, and PAH subcutaneously in 2 per cent sodium sulphate; urine was expelled by pressure and a terminal blood sample was collected by heart puncture. FW is taken as 0.8. C_{IN} and Tm_{PAH} in table x were recalculated by Corcoran *et al.* and C_{PAH} by the writer. The data as given by the authors are $C_{IN} = 0\ 36 \pm 0.04$ and $C_{PAH} = 2.31 \pm 0\ 18$ cc., $Tm_{PAH} = 0\ 10 \pm 0.01$ mg. per 100 sq. cm.; $C_{IN}/C_{PAH} = 0\ 157 \pm 0.023$; $C_{PAH}/Tm_{PAH} = 22\ 1 \pm 2.0$. They note that the C_{PAH}/Tm_{PAH} ratio is higher than in any other species yet reported, apparently because of the high value of C_{PAH}. No influence of urine flow on clearances was recorded.

* M Friedman's technique for obtaining renal clearances in rats has been criticized by Dicker and Heller,[417] to which criticism Friedman has replied[703]. In view of Lippman's[1161] results, it cannot yet be accepted with confidence that there is no tubular excretion of exogenous creatinine in the rat.

Lippman[1243] gave creatinine subcutaneously in 10 cc. of water. Urine was expelled by pressure, and blood drawn from the tail before the clearance period and collected by exsanguination at the end. Chemical determinations were made on pooled samples of plasma and urine. The influence of urine volume was not studied. He found that the endogenous creatinine chromogen clearance averaged 0.237 cc. per 100 gm. BW, in contrast to 0.915 cc for the exogenous clearance. The change in clearance value occurs in the plasma creatinine concentration range of 1 to 2 mg/100 cc. The exogenous creatinine clearance averaged 1.43 cc. per gm. KW.

Corcoran, Masson, Reuting, and Page[410] gave PAH-mannitol-creatinine solution subcutaneously in 2 doses of 1.7 cc/100 gm BW. Heparinized rats were restrained in a holder and catheterized under ether anesthesia, the bladder being rendered insensitive with intracaine Blood was collected from the tail after warming the animal at 45° C. for 3 min. before and at the end of the clearance period. They suggest that the greater variability in the data of Corcoran and Page[422] as compared with their present data presumably reflects the effects of light anesthesia and inaccuracy due to single blood sampling. They present data on 10 animals showing that, in successive determinations over a period of 4 weeks or more, C_{CR} and Tm_{PAH} remain fairly constant.

Lippman,[1244] in a second paper, compares clearances by two methods. In 'undisturbed' animals, which under ether have received 10 cc. of saline subcutaneously containing creatinine, urea, and PAH, urine was collected by having the animal sniff ether, and only a terminal blood sample was used The 'tail cutting' method is that given above. The 'undisturbed' clearance method gave average PAH, creatinine, and urea clearances of 3.38, 1.49, and 0.703 cc/100 gm. BW; by the 'tail cutting' method these figures were 2.63, 0.915, and 0.458. The 'undisturbed' clearance method gave PAH, creatinine, and urea clearances of 4.82, 1.06, and 2.27 cc/gm. KW; for the 'tail cutting' method these figures were 4.17, 0.669, and 1.43 cc. There was no relation between clearances and urine flow in either method. Recognizing that no method of clearance determination in the rat is entirely satisfactory, he recommends the 'tail cutting' method because the variability is less, and despite the depression in clearances involved in this technique.

Elsewhere Lippman[1246] asserts that, using the 'tail cutting' method, the subcutaneous administration of PAH in 10 cc. of saline depresses the simultaneous inulin clearance, the extent of this depression increasing in proportion to P_{PAH} Conversely, the subcutaneous administration of inulin depresses the PAH clearance roughly in proportion to the

value of P_{IN}. He believes that, with available preparations, C_{IN} and C_{PAH} or Tm_{PAH} cannot be determined simultaneously in this species.

Dicker, Heller, and Hewer[519] found that, in rats fed on a protein-deficient vegetable diet and suffering from severe hypoproteinemia, the filtration rate varies with the urine flow, contrary to Dicker and Heller's[514] observations on rats receiving a standard diet; while Dicker[510] has shown that saline trebles the filtration rate on a standard diet. Dicker[513] has re-examined this urine flow problem in greater detail. Using the technique of Dicker and Heller,[514] he administered 1 cc/100 gm. BW of inulin-saline solution intramuscularly and gave 50 cc/kg. of water *per os*. Urine was expelled by pressure and a terminal blood sample was used. The young animals were reared to the required weight (101 to 150 gm.) on the stipulated diet, and a series of adult rats were fed on the different diets for 9 weeks. They conclude that the plasma protein concentration of the adult rat varies with the amount of protein in the diet, and that in young and in adult rats with a plasma protein concentration below 6.8 gm/100 cc. the filtration rate increases with the urine flow. In adult rats fed on a diet containing 18 per cent or more of casein, and having a plasma protein concentration above 6.8 gm/100 cc., the filtration rate is independent of urine flow. High plasma protein concentrations are accompanied by higher mean rates of filtration.

Boss, Birnie, and Gaunt,[216] in a preliminary note, give an average creatinine clearance of 0.820 cc/min. per 100 gm. BW.

Watschinger and Werner,[2151] using Dicker and Heller's technique, report average inulin and diodrast clearances to be 0.58 and 1.89 cc/min. per 100 gm. BW, with a filtration fraction of 0.117.

Lotspeich,[1274] using the technique of S. M. Friedman *et al.*,[720] reports an average creatinine clearance of 0.513 cc/min. per 100 sq. m.

In view of all the variables—diet, saline, hydration, tail cutting, anesthesia (even 'light' as the authors say), the alleged effect of PAH on the inulin clearance and *vice versa*, and extrapolation of plasma concentrations and possible differences in strains—it is surprising that five groups of investigators arrive at about the same figure for the filtration rate (0.60 to 0.76 cc/min. per 100 gm. BW). The comparison of 'undisturbed' and 'tail cutting' methods by Lippman must await clarification of some of the other variables, and until that time figures for the effective renal plasma flow in the rat must remain uncertain.

Taking the best figure for the filtration rate from table x as 0.6 cc/100 gm. BW, 8.0 gm. of kidney per kg (*vide infra*) gives 0.75 cc/min. per gm. KW. (Lippman[1243,1244] gives 1.49 and 1.43 cc., but his figures are out of line with all others, as shown in table x.) The corresponding best

figure for renal plasma flow appears to be 2.2 cc/100 gm. BW or 2 75 cc/gm KW, and for TmPAH 0.30 mg/100 gm BW and 0.375 mg/gm. KW. Taking the surface area on a 200 gm rat as 0.0301 sq. m., the data above give a filtration rate of 39 9, plasma flow of 146 cc., and TmPAH of 20 mg/sq. m.

The whole blood urea clearance in the rat is reported by Farr and Smadel [677] to be 10 9 ± 3 1 cc., and by Herrin [850] as 19 3 cc/sq m The average figure obtained by MacKay and Roulston [1184] is 0.33 per gm. KW (using decapsulated kidneys).

RABBIT

Hayman and Starr [812] concluded by intravital staining that the number of active glomeruli in the anesthetized (urethane and sometimes ether) rabbit varies widely, and may be increased to a maximal extent by caffeine and salt solution and reduced by adrenalin and other agencies which induce vasoconstriction No correlation was observed between the number of active glomeruli and the volume of the kidney The complexity of such a study is revealed by the following functional studies, and by the discussion of the juxtamedullary circulation in chapter xxv.

Kaplan and Smith [1000] reported that in the rabbit the inulin and creatinine clearances (which are identical in this species) increase with urine flow These investigators administered water by stomach and kept their animals restrained on an animal board. They found that, if water in quantities greater than 3 successive doses of 40 cc/kg at 30 min. intervals is given, the animal is apt to develop oliguria which is frequently followed by convulsions and death (water intoxication?) Reviewing their own data and the observations of others on the injection of dyes, etc., they concluded that in this species, contrary to the situation in the dog and man, hydration is accompanied by a marked increase in glomerular activity.

W W Smith,[1667] however, found no relation between the filtration rate or diodrast clearance and the urine flow at values of the latter ranging from 0 4 to 7 0 cc/min. per 100 gm KW (0 072 to 1.26 cc/min per kg BW) Mannitol diuresis increased the filtration rate by 20 to 50 per cent and the diodrast clearance by 15 to 75 per cent, but this fact has little bearing on the question of glomerular activity in relation to hydration *per se* No explanation of the discrepancy between her results and those of Kaplan and Smith was apparent, as she noted. The average inulin clearance in 8 rabbits was 0 66 cc. (0.38 to 0.94) and the average diodrast clearance 2.50 cc/gm. KW (1 23 to 3 78), and the average filtration fraction 0.273 (0.19 to 0.40).

An apparent relation between filtration rate and urine flow in the rabbit was, however, again recorded by Dicker and Heller,[514] Wilkinson and McCance,[2221] and Forster.[678] The latter found that fair urine flows could be obtained in rabbits by feeding them an abundance of cabbage and other green food for 24 hr. before an experiment. Under these conditions, he found no change in filtration rate or renal plasma flow dur-

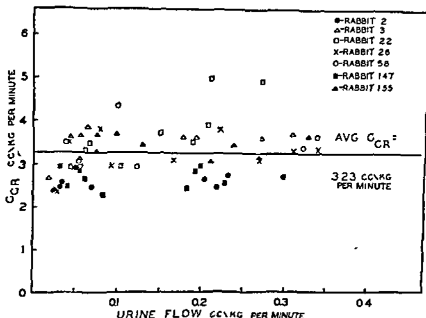


FIGURE 97. Relationship between filtration rate and urine flow in undisturbed rabbits. *A 16-fold increase in urine flow* during water diuresis is possible without significant variation in the filtration rate (Brod and Sirota [265])

ing moderate variations in urine flow, and no differences were observed in renal function as between the prone and sitting positions However, *the administration of water (50 cc/kg) to rabbits* that had been kept on a diet of dry food led to an increase in filtration rate (14 3 to 20 2 cc/min.) and renal plasma flow (70 to 104 cc/min) in the next hour. Glucose Tm also increased from 37 to 64 mg., parallel with the increase in filtration rate, and Forster concluded that the increased renal function was accompanied by recruitment of inactive glomeruli. *Introduction* of mannitol into the infusion had no effect on filtration rate, renal plasma flow, or glucose Tm, although it greatly increased the urine flow by reducing the reabsorption of water. Theophylline similarly had no

effect on filtration rate and renal plasma flow, though it produced diuresis Forster inferred that not all the glomeruli in the rabbit are active and that water diuresis increases glomerular activity, mannitol and theophylline having no such effect.

Brod and Sirota,[261] on re-examining the problem, concluded that the results obtained by Kaplan and Smith were attributable to renal vasoconstriction induced by excitement when water was administered by stomach tube, this vasoconstriction is of course accompanied by oliguria and as the vasoconstriction recedes the filtration rate and urine flow increase together. The presumed relationship between filtration rate and urine flow observed by Kaplan and Smith and others they considered to be a fortuitous consequence of autonomic excitation and renal ischemia If precautions were used to prevent autonomic excitation, it was found that the filtration rate remained unchanged despite a sixteenfold variation in urine flow between 0 02 to 0.32 cc/min per kg (c.0.1 to 1 5 cc/min. per sq. m.), and regardless whether the urine flow was increasing or decreasing (fig. 97). Although the strength of the stimulus required to produce emotional disturbance varied with the excitability of individual animals, fright or painful stimuli of sufficient intensity always caused antidiuresis by renal vasoconstriction, as a result of which there was a marked reduction in renal plasma flow and filtration rate with little change in the creatinine U/P ratio. During this renal ischemia, water intoxication with convulsions and rapid death was easily obtained and many animals died in convulsions *

Renal denervation did not appreciably reduce the renal response to the usual excitatory stimuli. Adrenalin in large doses (400 μ) had the same action as emotional excitation, smaller doses (50 to 120 μ) failing to have consistent effects. Dibenamine (5 mg/kg. intravenously) did not block the vasoconstriction in 3 animals with renal nerves intact, but in 3 out of 4 animals with denervated kidneys the renal plasma flow and filtration rate increased immediately after its administration. Pitressin in physiological doses (2 milliunits intravenously) produced antidiuresis with little effect on the renal plasma flow.

Brod and Sirota conclude with W W. Smith that in the rabbit, as in the dog and man, uncomplicated water diuresis is mediated by changes in the tubular reabsorption of water with little or no contribution from changing glomerular activity. This conclusion is supported by the report of Wills and Main [227] that in rabbits anesthetized with nembutal the filtration rate does not vary with urine flow

Dicker and Heller [118] have replied to Brod and Sirota that the condi-

* This might be called psychosomatic death

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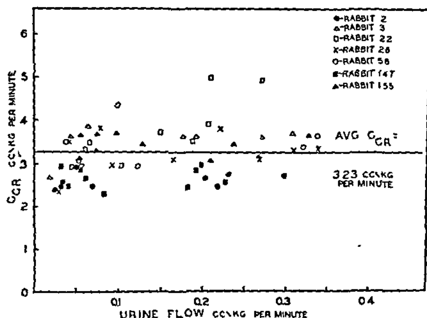


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Brod and Sirota,[268] on re-examining the problem, concluded that the results obtained by Kaplan and Smith were attributable to renal vasoconstriction induced by excitement when water was administered by stomach tube; this vasoconstriction is of course accompanied by oliguria and as the vasoconstriction recedes the filtration rate and urine flow increase together. The presumed relationship between filtration rate and urine flow observed by Kaplan and Smith and others they considered to be a fortuitous consequence of autonomic excitation and renal ischemia. If precautions were used to prevent autonomic excitation, it was found that the filtration rate remained unchanged despite a sixteen-fold variation in urine flow between 0.02 to 0.32 cc/min per kg (c 0.1 to 1.5 cc/min per sq m), and regardless whether the urine flow was increasing or decreasing (fig. 97). Although the strength of the stimulus required to produce emotional disturbance varied with the excitability of individual animals, fright or painful stimuli of sufficient intensity always caused antidiuresis by renal vasoconstriction, as a result of which there was a marked reduction in renal plasma flow and filtration rate with little change in the creatinine U/P ratio. During this renal ischemia, water intoxication with convulsions and rapid death was easily obtained and many animals died in convulsions.*

Renal denervation did not appreciably reduce the renal response to the usual excitatory stimuli. Adrenalin in large doses (400 μ) had the same action as emotional excitation, smaller doses (50 to 120 μ) failing to have consistent effects. Dibenamine (5 mg/kg intravenously) did not block the vasoconstriction in 3 animals with renal nerves intact, but in 3 out of 4 animals with denervated kidneys the renal plasma flow and filtration rate increased immediately after its administration. Pitressin in physiological doses (2 milliunits intravenously) produced antidiuresis with little effect on the renal plasma flow.

Brod and Sirota conclude with W. W. Smith that in the rabbit, as in the dog and man, uncomplicated water diuresis is mediated by changes in the tubular reabsorption of water with little or no contribution from changing glomerular activity. This conclusion is supported by the report of Wills and Main[2227] that in rabbits anesthetized with nembutal the filtration rate does not vary with urine flow.

Dicker and Heller[618] have replied to Brod and Sirota that th—

* This might be called psychosomatic death.

tions of their original experiments were not such as to be interpreted in this manner. Reanalysis of their data leads them to affirm that in the adult rabbit changes in glomerular activity play an important role in regulating water excretion during hydration as well as changes in tubular reabsorption They point out that such glomerular participation has been demonstrated not only in the Amphibia but in young and newborn rats and newborn guinea pigs, and was indicated by earlier studies on human infants. The implication is that the kidney of the adult rabbit behaves toward hydration in an infantile manner.

Thus there is at the moment wide disagreement on renal function in this species Until the issues have been resolved, we shall tentatively accept Brod and Sirota's average data. Their averages for 69 clearances (each an average of 3 periods) on 21 male rabbits, including control observations, were: creatinine 3.12 ± 0 058 cc., PAH clearance 18.2 ± 3.4 cc/kg , filtration fraction = 0.17. Taking the KW/BW ratio as 6.4 (*vide infra*), these data give 0.488 and 2 85 cc/gm. KW. W. W. Smith's[190a] direct ratios of 0.66 and 2 5 cc/min. per gm. KW (as used in table XIV, p 568) are probably more reliable calculations (although both used Carworth Farms white rabbits), since they do not involve an indirect calculation. On a surface area basis, Brod and Sirota's figures give a filtration rate of 50 2 ± 9.2 cc. and a renal plasma flow of 296 ± 59 cc/min per sq. m.

In anesthetized (urethane) rabbits, Laake[1183] obtained much lower values: his average filtration rate was 24.4 ± 6.5 cc/sq. m (10.38 to 38 86) In unanesthetized rabbits the average diodrast clearance was 194.3 ± 3 8 cc. (187 to 202) and Tm_D averaged 33 45 ± 2 13 mg. of iodine per sq m. Tm_G averaged 78.71 ± 13 4 mg/sq. m. (Self-depression of the diodrast clearance begins at a plasma concentration of about 25 mg. of iodine per 100 cc.)

The whole blood urea clearance in the rabbit during urea diuresis averages 0 294 cc/gm. kidney, or 25.5 cc/sq. m.[2043]

The creatinine clearance/Tm_G ratio is about 0 27.[1952]

The writer has heard pathologists and others comment that the rabbit gives highly variable results in certain experimental procedures He adheres to the prejudice that the species possesses a degree of autonomic instability which leads to intense sympathetic discharge under circumstances in which the dog and man remain quiescent.

CAT

Wirz[2249] records the inulin clearance in unanesthetized cats as ranging from 33 to 94 cc/sq. m. (SA = 10 $BW^{0.66}$) with a mean value of about

50 cc The filtration rate appears to be independent of the urine flow. In this species the inulin U/P ratio may reach values as high as 700.

DOG

Corcoran and Page[411] report 77 observations on 7 female dogs maintained on 1 daily feeding of dog biscuit (Purina Dog Chow) and weekly supplements of lean meat. All observations were made after 18 hr. of fasting and at least 36 hr. after meat had been fed. No water was administered to produce diuresis, but sodium sulphate (2 per cent) was added to the priming and sustaining infusion in order to insure moderate urine flows One would say that the dogs were 'basal' and unhydrated. The mean data were: filtration rate 69 ± 14 8, renal plasma flow (from phenol red) 250 ± 61, whole blood 460 ± 118 cc/min per sq m, the last two figures being corrected for E_{PR} and the whole blood figure agreeing with that calculated from E_{IN} by 1 per cent The mean filtration fraction was 0.297. The figure for renal plasma flow agrees well with that cited by Houck,[1037] but the filtration rate is lower Corcoran, Taylor, and Page[432] give the average ratios RBF/Tm_D = 23.78 ± 3 65, C_{IN}/Tm_D = 2.68 ± 0 402 The last ratio is close to that in women, 2 81 ± 0 535, and identical with that in men, 2 63 ± 0.344, while the first is slightly less than the value in man estimated on a hematocrit of 0 46 (26 3 female and 25 9 male). (This similarity in these ratios is surprising, in view of the fact that the dog kidney does not excrete as much PAH per unit of filtrate as does man Thus the Tm_{PAH}/C_F ratio in the dog is 0 236, whereas in man this ratio is 0.624 (table XII). The data indicate a deficit in the dog relative to PAH excretion not applicable to diodrast.

Houck has tabulated the creatinine and PAH clearances in 75 mongrel female dogs maintained on a mongrel diet of dog biscuit, hospital scraps, etc, the data representing observations collected in the writer's laboratory by various investigators over a period of several years These data are illustrated in figures 98 and 99 against the 70 per cent ellipse * with corresponding data in man (fig 100) The average figure for filtration rate is 84 4 ± 19 1 and for renal plasma flow 266 ± 66 cc/min per sq m, or 4 29 ± 1 01 and 13 51 ± 3 26 cc/min per kg. BW The average filtration fraction is 0 317. Allowing for 90 per cent extraction of PAH, the true filtration fraction would be 0.285. It is of interest that Medes and Herrick,[1423] using the thermostromuhr method, obtained a filtration fraction of 0 31, and Van Slyke *et al.*,[2092] using E_{CR} and E_{IN} in the explanted kidney with the other kidney removed, obtained 19 9

* See footnote page 547 for the derivation of this ellipse.

and 22.3 per cent. The last two figures are unquestionably lowered by renal hyperemia associated with hypertrophy of the remaining kidney.

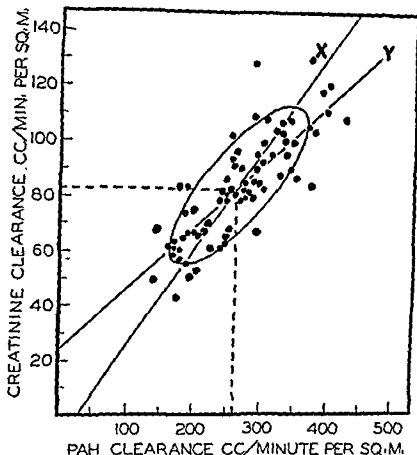


FIGURE 98. Comparison of filtration rate and renal plasma flow as related to body surface area in 75 normal dogs. Each point represents a different dog and is the average of from 1 to 19 clearance observations. Dashed lines are the means for each function. The ellipse delimits the area of a scatter diagram within which 70 per cent of the points may be expected to fall by chance alone, assuming normal bivariant distribution. X represents the regression of renal plasma flow on filtration rate (i e the variation along the *x* axis for a given value of *y*) and *vice versa*. (Houck [1037])

Stamler, Katz, and Rodbard,[1977] in their study of normotensive and hypertensive dogs, report for 6 normal male dogs an average filtration rate of 104 ± 15 (86 to 127), a PAH clearance of 295 ± 58 cc/min. per sq. m. (range 86 to 127), with a filtration fraction of 0.353. These values

are slightly higher than those of Houck on female dogs ... ences are not statistically significant. The average ... perhaps significantly higher.

Moustgaard[1483] on 118 dogs records the average ... 0 64 ± 12 and the plasma flow as 1.91 cc/min per ... tion fraction as 0 335

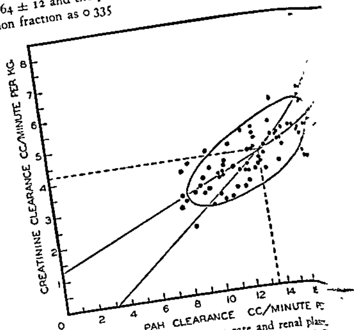


FIGURE 99 Comparison of filtration rate and renal plasm... body weight in 75 normal dogs See legend of figure 98 ...

Taking the KW/BW ratio as 7 1 gm/kg. (*vide in*... for filtration rate and renal plasma flow would be ... cc/gm of kidney Both figures are in remarkable ag... of Moustgaard, and we have used the average of the ...

The writer has assembled the data on TmPAH ... Gaudino and Levitt,[750] Handley, Telford, and La... Sigafoos, and La Forge,[901] and White, Heinbecker ... other data kindly supplied by Drs. Richardson, Sch... to supply the statistics given in table XI.* It may b...

* The writer is indebted to Mr Charles Crowder, Jr ... and for many others cited in subsequent pages

TABLE XI

Tm_{PAH} *in Female Dogs*

	Number	Mean	σ	100 σ/m
C_{CR}/kg.	67	3.84 cc.		
C_{PAH}/kg.	51	12.5 cc.		
Tm_{PAH}/kg.	83	0.97 mg.	0.091	9 4
C_{CR}/Tm_{PAH}	67	4.24	0 66	15.6
C_{PAH}/Tm_{PAH}	51	12 9	2.43	18.8

efficient of variation of Tm_{PAH} per kg. (9.4 per cent) is the smallest one on record in renal physiology.

Houck's[1037] average ratio of sq. m. surface area to kg. body weight for 75 dogs is 19.7, which would give Tm_{PAH} = 19.1 mg/min. per sq. m., while this value would be 0.137 mg/gm. KW.

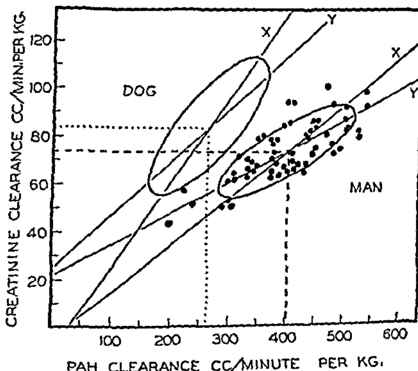


FIGURE 100. Comparison of filtration rate and renal plasma flow, as related to body surface area, in dog and man. The ellipse and lines of regression for the dog are transposed from figure 99 *Those for man were calculated from the* data of Smith *et al.*[1031] (Houck[1037])

TABLE XII

Statistics on Filtration Rate and Renal Blood Flow in Man

Clearances, Tm_D, and Tm_{PAH} corrected to 1 73 sq m. and Tm_D and Tm_{PAH} corrected to 98 5° F. rectal temperature. Figures in parentheses show the number of subjects studied. No subject is counted twice Figures in bold-face type show weighted averages.

MALES

Method	Age range years	Plasma clearances: Inulin cc/min.	Plasma clearances: PAH cc/min	Renal blood flow cc/min	Tm_{PAH} mg/min	Filtration fraction × 100	C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	Authors
CI	16–49	(34) 124 1 ±25 8	(30) 654 ±163		(35) 79 8 ±16 7	(31) 19 2 ±3 5	(30) 8 44 ±2 45	(33) 1 6 ±0 44	Smith (see text)
CI	21–32		(9) 613 ±107						Chapman *et al* [153]
CI		(8) 130 ±15 4	(8) 628 ±44 8		(8) 65 6 ±8 7				Brun *et al* [278]
			(8) 603 ±84 4						Heller *et al* (see Chapman *et al*)
Weighted average					**(43) 77 2**		**(30) 8 44**	**(33) 1 6**	
			Diodrast		**Tm_D**		**C_D/Tm_D**	**$C_{IN}Tm_D$**	
CI	16–60	(67) 131 ±21 5	(61) 697 ±136	(61) 1209 ±256	(40) 51 8 ±8 73	(61) 19 0 ±2 44	(34) 14 0 ±2 16	(40) 2 63 ±0 344	Smith & Smith *et al* [1931 1939]
CI	20–50	(36) 124 ±13 3	(36) 449 ±40 1‡	(36) 853 ±63 9‡		(36) 27 6 ±0 5‡			Hogeman[1024]
CI	20–39	(18) 119 ±14 4	(18) 631 ±99 7		(18) 52 8 ±9 25				Shock *et al.* (pers. com., see text)
CI	–40	(17) 117	(17) 544	(17) 1010	(9) 40 1	(11) 20 5	(9) 13 6†	(9) 2 91†	Findley *et al* [646]
CI	21–25	(10) 125 ±4 4	(10) 600 ±106		(10) 50 6 ±6 5	(10) 21 4 ±3 48	(10) 12 1 ±2 3	(10) 2 51 ±0 332	Brun *et al* [276]
CI	22–56	(7) 117		(7) 1060	(5) 40 2	(7) 18 2	(5) 16 2	(5) 3 08	Foà *et al* [665]
CI	19–41	(6) 128	(6) 688			(6) 18 6			Steinitz[1898]
CI	22–50	(4) 124	(6) 761	(6) 1288		(4) 17 8			Friedman *et al* [714]
SC			(12) 617‡						Hilden[1001]
SC	22–31		(5) 552‡						Hilden [1000]
SC			(6) 566‡	(6) 987‡	(6) 39‡	(6) 15 0‡	(6) 15 9‡		Foà *et al* [664]
CI		(26) 126 ±17 1							Berger *et al* [128]
CI	18–45	(25) 140 ±32							Josephson *et al* [1084]
Weighted average		**(258) 127**	**(179) 655**	**(91) 1166**	**(82) 49 9**	**(130) 19 3**	**(58) 13 8**	**(64) 2 7**	

Method	Age	C_{IN}	C_{PAH} / C_D		Tm		C/Tm	C_{IN}/Tm	Reference
FEMALES									
			PAH		Tm_{PAH}		C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	
CI		(16) 108.8±13.5	(11) 597±153		(16) 77.2±10.8	(11) 19.4±3.9	(11) 7.85±1.46	(16) 1.43±0.20	Smith (see text)
Weighted average					(16) 77.2		(11) 7.85	(16) 1.43	
			Diodrast		Tm_D		C_D/Tm_D	C_{IN}/Tm_D	
CI	20–50	(20) 110±12.8	(20) 436±10‡	(20) 763±66.4‡	(14) 42.6±9.46	(20) 27.4±0.7‡	(14) 14.2±2.36	(14) 2.81±0.56	Hogeman[1024]
CI	16–55	(21) 117±15.6	(17) 594±102	(17) 982±184	(10) 44.2±4.83	(17) 20.2±3.1	(10) 14.2±2.54	(10) 2.69±0.412	Smith & Smith et al[1981,1989]
CI	19–27	(10) 118±13.9	(10) 628±100			(10) 18.0±1.74			Brun et al[275]
CI	25–40	(5) 126	(5) 669	(5) 986		(5) 19.0			Friedman et al[714]
CI			(9) 518	(9) 836					Chesley et al[373]
SC		(13) 127	(6) 610‡			(6) 19.9‡			Brun et al[281]
SC			(12) 608‡			(4) 19.0‡			Hilden[1001]
IM		(6) 114	(4) 609‡						Brun et al[282]
IM	19–30		(5) 595‡	(5) 940‡	(5) 36.0‡				Hilden[1000]
SC			(5) 566‡						Foà et al[864]
Weighted average		(91) 118	(57) 600	(31) 940	(29) 42.0	(43) 19.5	(34) 14.3	(24) 2.76	
MIXED SEXES									
			PAH		Tm_{PAH}		C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	
CI		(50) 116.5±28.1	(40) 640±164		(40) 78.9±13.2	(40) 18.2	(41) 8.28±2.2	(49) 1.54±0.4	Smith (see text)
CI		(32) 129±40	(35) 626±165			(32) 20.6±5.6			Merrill[1418]
SC		(6) 133	(6) 701			(6) 19.1			Aas et al[2]
		(13) 129*‡	(13) 538‡						Hamburger et al[892]
Weighted average				(6) 1165	(40) 78.9		(41) 8.28	(49) 1.54	
			Diodrast		Tm_D		C_D/Tm_D	C_{IN}/Tm_D	
CI	20–50	(56) 122±13.2	(56) 444±41.6‡		(4) 53.2	(56) 27.5±3.0‡	(?) 15.3±6.4	(?) 3.01±0.64	Hogeman[1024]
CI		(8) 120	(8) 537			(8) 23			Black et al[184]
CI	18–54	(5) 148	(4) 738		(?) 49.4±8.8	(4) 21.2			Talbott et al[2042]
CI		(?) 128±20.2	(?) 674±128	(?) 1075±233	(?) 53±11	(?) 19±2.4			Corcoran et al[432]
CI	2–12	(?) 133±14.9	(?) 695±183			(?) 19±2			Galán et al[734]
SC		(15) 123‡							Ahlborg[24]
Weighted average		(157) 123	(93) 634	(6) 1165	(4) 53.2	(90) 19.7			

CI = constant intravenous infusion, SC = subcutaneous injection, IM = intramuscular injection.
* Mannitol.
† Not on same individuals.
‡ Omitted from weighted means

TABLE XII

Statistics on Filtration Rate and Renal Blood Flow in Man

Clearances, Tm_D, and Tm_{PAH} corrected to 1 73 sq m. and Tm_D and Tm_{PAH} corrected to 98 5° F. rectal temperature. Figures in parentheses show the number of subjects studied. No subject is counted twice. Figures in bold-face type show weighted averages.

MALES

Method	Age range years	Plasma clearances: Inulin cc/min	Plasma clearances: PAH cc/min	Renal blood flow cc/min	Tm_{PAH} mg/min	Filtration fraction × 100	C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	Authors
CI	16–49	(34) 124.1 ±25 8	(30) 654 ±163		(35) 79 8 ±16 7	(31) 19 2 ±3 5	(30) 8 44 ±2 45	(33) 1 6 ±0 44	Smith (see text)
CI	21–32		(9) 613 ±107						Chapman *et al* [352]
CI		(8) 130 ±15 4	(8) 628 ±44 8		(8) 65 6 ±8 7				Brun *et al* [278]
			(8) 603 ±84 4						Heller *et al* (see Chapman *et al*)
Weighted average					**(43) 77 2**		**(30) 8 44**	**(33) 1 6**	
			Diodrast		Tm_D		C_D/Tm_D	C_{IN}/Tm_D	
CI	16–60	(67) 131 ±21 5	(61) 697 ±136	(61) 1209 ±256	(40) 51 8 ±8 73	(61) 19 0 ±2 44	(34) 14 0 ±2 16	(40) 2 63 ±0 344	Smith & Smith *et al* [1031, 1039]
CI	20–50	(36) 124 ±13 3	(36) 449 ±40 1‡	(36) 853 ±63 9‡		(36) 27 6 ±0 5‡			Hogeman[1024]
CI	20–39	(18) 119 ±14 4	(18) 631 ±99 7		(18) 52 8 ±9 25				Shock *et al* (pers com, see text)
CI	–40	(17) 117	(17) 544	(17) 1010	(9) 40 1	(11) 20 5	(9) 13 6†	(9) 2 91†	Findley *et al* [648]
CI	21–25	(10) 125 ±4 4	(10) 600 ±106		(10) 50 6 ±6 5	(10) 21 4 ±3 48	(10) 12 1 ±2 3	(10) 2 51 ±0 332	Brun *et al* [278]
CI	22–56	(7) 117		(7) 1060	(5) 40 2	(7) 18 2	(5) 16.2	(5) 3 08	Foà *et al* [665]
CI	19–41	(6) 128	(6) 688			(6) 18 6			Steinitz[1999]
CI	22–50	(4) 124	(6) 761	(6) 1288		(4) 17 8			Friedman *et al* [714]
SC			(12) 617‡						Hilden[1001]
SC	22–31		(5) 552‡						Hilden[1000]
SC			(6) 566‡	(6) 987‡	(6) 39‡	(6) 15 0‡	(6) 15 9‡		Foà *et al* [664]
CI		(26) 126 ±17 1							Berger *et al* [128]
CI	18–45	(25) 140 ±32							Josephson *et al* [1085]
Weighted average		**(258) 127**	**(179) 655**	**(91) 1166**	**(82) 49 9**	**(130) 19 3**	**(58) 13 8**	**(64) 2 7**	

FEMALES									
			PAH		Tm_{PAH}		C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	
CI Weighted average		(16) 108.8±13.5	(11) 592±153		(16) 77.2±10.8	(11) 10.4±3.9	(11) 7.85±1.46	(16) 1.43±0.20	Smith (see text)
					(16) 77.2		(11) 7.85	(16) 1.43	
			Diodrast		Tm_D		C_D/Tm_D	C_{IN}/Tm_D	
CI	20–50	(20) 110±12.8	(20) 436±10‡	(20) 763±66.4‡	(14) 42.6±9.46	(20) 27.4±0.7‡	(14) 14.2±2.36	(14) 2.81±0.56	Hogeman[1024]
CI	16–55	(21) 117±15.6	(17) 594±102	(17) 982±184	(10) 44.2±4.83	(17) 20.2±3.1	(10) 14.2±2.54	(10) 2.69±0.412	Smith & Smith et al[1031,1029]
CI	19–27	(10) 118±13.9	(10) 628±100			(10) 18.9±1.74			Brun et al[276]
CI	25–40	(5) 120	(5) 669	(5) 986		(5) 19.0			Friedman et al[714]
CI			(9) 518	(9) 836					Chesley et al[372]
SC		(13) 127	(6) 610‡			(6) 19.9‡			Brun et al[281]
SC			(12) 608‡						Hilden[1001]
IM		(6) 114	(4) 609‡			(4) 19.0‡			Brun et al[282]
IM	19–30		(5) 595‡						Hilden[1000]
SC			(5) 566‡	(5) 940‡	(5) 36.0‡				Foà et al[664]
Weighted average		(91) 118	(57) 600	(31) 940	(29) 42.0	(43) 19.5	(24) 14.3	(24) 2.76	
MIXED SEXES									
			PAH		Tm_{PAH}		C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	
		(50) 116.5±28.1	(40) 640±164		(40) 78.9±13.2	(40) 18.2	(41) 8.28±2.2	(49) 1.54±0.4	Smith (see text)
CI		(32) 120±40	(35) 626±165			(32) 20.6±5.6			Merrill[1418]
CI		(6) 133	(6) 701	(6) 1165		(6) 19.1			Aas et al[2]
SC		(13) 129*‡	(13) 538‡						Hamburger et al[892]
Weighted average					(40) 78.9		(41) 8.28	(49) 1.54	
			Diodrast		Tm_D		C_D/Tm_D	C_{IN}/Tm_D	
CI	20–50	(56) 122±13.2	(56) 444±41.6‡			(56) 27.5±3.0‡			Hogeman[1024]
CI		(8) 120	(8) 537			(8) 23			Black et al[184]
CI	18–54	(5) 148	(4) 738		(4) 53.2	(4) 21.2			Talbott et al[1043]
CI		(?) 128±20.2	(?) 674±128	(?) 1075±233	(?) 49.4±8.8	(?) 19±2.4	(?) 15.3±6.4	(?) 3.01±0.64	Corcoran et al[432]
CI	2–12	(?) 133±14.9	(?) 695±183		(?) 53±11	(?) 19±2			Galán et al[735]
SC		(15) 123‡							Ahlborg[28]
Weighted average		(157) 123	(93) 634	(6) 1165	(4) 53.2	(90) 19.7			

CI = constant intravenous infusion, SC = subcutaneous injection, IM = intramuscular injection.
* Mannitol
† Not on same individuals.
‡ Omitted from weighted means.

TABLE XII

Statistics on Filtration Rate and Renal Blood Flow in Man

Clearances, Tm_D, and Tm_{PAH} corrected to 1.73 sq. m. and Tm_D and Tm_{PAH} corrected to 98.5° F. rectal temperature. Figures in parentheses show the number of subjects studied. No subject is counted twice. Figures in bold-face type show weighted averages.

MALES

Method	Age range years	Plasma clearances: Inulin cc/min	Plasma clearances: PAH cc/min	Renal blood flow cc/min	Tm_{PAH} mg/min	Filtration fraction × 100	C_{PAH}/Tm_{PAH}	C_{IN}/Tm_{PAH}	Authors
CI	16–49	(34) 124.1±25.8	(30) 654±163		(35) 79.8±16.7	(31) 19.2±3.5	(30) 8.44±2.45	(33) 1.6±0.44	Smith (see text)
CI	21–32		(9) 613±107		(8) 65.6±8.7				Chapman et al[362]
CI		(8) 130±15.4	(8) 628±44.8						Brun et al[278]
			(8) 603±84.4						Heller et al (see Chapman et al)
Weighted average					**(43) 77.2**		**(30) 8.44**	**(33) 1.6**	
			Diodrast		**Tm_D**		**C_D/Tm_D**	**C_{IN}/Tm_D**	
CI	16–60	(67) 131±21.5	(61) 697±136	(61) 1209±256	(40) 51.8±8.73	(61) 19.0±2.44	(34) 14.0±2.16	(40) 2.63±0.344	Smith & Smith et al[1931,1939]
CI	20–50	(36) 124±13.3	(36) 449±40.1‡	(36) 853±63.9‡		(36) 27.6±0.5‡			Hogeman[1024]
CI	20–39	(18) 119±14.4	(18) 631±99.7		(18) 52.8±9.25				Shock et al (pers com., see text)
CI	–40	(17) 117	(17) 544	(17) 1010	(9) 40.1	(11) 20.5	(9) 13.6†	(9) 2.91†	Findley et al[648]
CI	21–25	(10) 125±4.4	(10) 600±106		(10) 50.6±6.5	(10) 21.4±3.48	(10) 12.1±2.3	(10) 2.51±0.332	Brun et al[276]
CI	22–56	(7) 117		(7) 1060	(5) 40.2	(7) 18.2	(5) 16.2	(5) 3.08	Foà et al[665]
CI	19–41	(6) 128	(6) 688			(6) 18.6			Steinitz[1899]
CI	22–50	(4) 124	(6) 761	(6) 1288		(4) 17.8			Friedman et al[714]
SC			(12) 617‡						Hilden[1001]
SC	22–31		(5) 552‡	(6) 987‡	(6) 39‡	(6) 15.0‡	(6) 15.9‡		Hilden[1000]
SC			(6) 566‡						Foà et al[664]
CI		(26) 126±17.1							Berger et al[122]
CI	18–45	(25) 140±32							Josephson et al[1088]
Weighted average		**(258) 127**	**(179) 655**	**(91) 1166**	**(82) 49.9**	**(130) 19.3**	**(58) 13.8**	**(64) 2.7**	

Statistical Analysis of Renal Function

Statistical analyses of the filtration rate, renal plasma flow, and Tm_D have been recorded by numerous investigators and are summarized in table XII.

A limited number of data are available for the description of renal function relative to Tm_{PAH}. The writer has recalculated Tm_{PAH} of table I of Chasis *et al.*[362] and Bolomey *et al.*[207] with appropriate correction of Tm_{PAH} for the chemical error in the mannitol method,[86] and combined these with table 2 of Chasis *et al.*[362] and with 29 observations supplied by Michie and 8 observations supplied by Earle, to obtain the data for mixed and separate sexes given in table XII. From these data a 70 per cent ellipse * has been calculated for the mixed sexes, as shown in figures 101 and 102. The number of observations available for the separate sexes does not warrant a separate treatment of this ellipse.

The basic data for the reconstruction of these ellipses are given in the legend of figures 101 and 102. The number of observations

4 or more for Tm Technical errors as well as physiological changes, which might otherwise be overlooked, are thus frequently revealed

* The area on a scatter diagram within which we may theoretically expect 70 per cent of the observations to fall by chance alone is an ellipse formed by the equation

$$\chi^2 = \left(\frac{x^2}{\sigma_x^2} - \frac{2rxy}{\sigma_x\sigma_y} + \frac{y^2}{\sigma_y^2}\right)\frac{1}{1 - r^2},$$

[illegible]

above, x is the distance from mx along the x axis, y is the distance from my along the y axis, σ_x and σ_y are the standard deviations of the distribution in the x and y direction respectively, and r is the coefficient of correlation x is determined for various values of y by resolving the above equation in the quadratic.

$$x = \frac{-ay}{2} \pm \sqrt{\left(\frac{a^2}{4} - b\right)y^2 - c}$$

and writing

$$a = -\frac{2r\sigma_x}{\sigma_y}, \quad b = \frac{\sigma_x^2}{\sigma_y^2}, \quad c = -(1 - r^2)\chi^2\sigma_x^2$$

An ellipse on a scatter diagram within which 70 per cent of the observations may be expected to fall by chance corresponds roughly to a distance from -1σ to $+1\sigma$ on a linear scale for 1 variable (68 per cent of the observations).

The mean values of renal clearances at their peak levels in determinations extending over a 24 hr. period, as recorded by Sirota, Baldwin, and Villarreal,[1904] are lower than the short period clearance data recorded in table XII; in 16 male subjects the inulin clearance averaged 119 ± 23 cc., and in 10 male subjects the PAH clearance averaged 597 ± 124 cc. These subjects were allowed water *ad libitum* but were not hydrated prior to observation. The series is small, but perhaps indicates that the routine hydration used in short period clearance determination may increase both the filtration rate and renal plasma flow significantly.

Clearance Variation

Koepf, Hubbard, and Loomis[1145] record a statistical analysis of simultaneous inulin and diodrast clearances in 79 separate 15 min. test periods upon 19 subjects. The inulin clearance showed greater constancy than did the diodrast clearance, which the authors attribute to closer regulation of the filtration rate.

Davies and Shock[473] have made clearance determinations on each of 2 days, separated by 1 week to 1 year intervals, on 40 subjects ranging from 27 to 89 years of age. Older subjects showed less variation, both from period to period on the same day, and from day to day, than did younger ones They find evidence of a systematic decrease in measurements made in successive periods on the same day. (It has been the experience of investigators in the writer's laboratory that the filtration rate and renal plasma flow tend to drift downward in long tests, a phenomenon which has been loosely attributed to discomfort, restlessness, and fatigue on the part of the patient, though decreasing hydration may play a part) Measurements in successive collection periods on the same individual on the same day will group themselves around the average value with a standard deviation of the mean of 6.1 cc for C_{IN}, 33 cc. for C_D, and 2.9 mg. of iodine for Tm_D, all per 1.73 sq. m. The variation of an individual from day to day is significantly greater than the experimental (period to period) variation, as might be anticipated Davies and Shock suggest, because of the large individual day-to-day variation, that the number of collection periods in any one test makes only a moderate contribution to the total variance, and increasing the number of periods beyond 2 or 4 does not greatly reduce the error.*

[illegible] technique [illegible] a high [illegible] writer [illegible] would take the liberty to suggest that others who may not [illegible] t of an equal competence would do well to rely on 3 periods for the filtration rate and

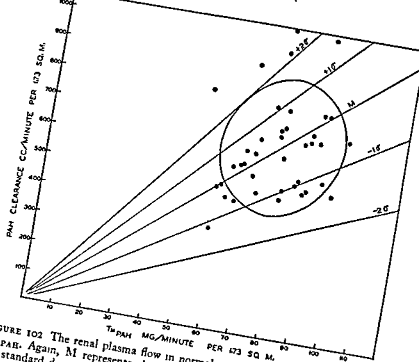


FIGURE 102 The renal plasma flow in normal man (mixed sexes) as related to Tm_{PAH}. Again, M represents the mean ratio C_{PAH}/Tm_{PAH}, ± multiples of the standard deviation The ellipse is calculated to contain 70 per cent of the observations (corresponding to $\pm\sigma$) and actually contains 80 per cent

The basic data used are C_{PAH} = 640 ± 164 and Tm_{PAH} = 78.3 ± 13 4 (40 observations), C_{PAH}/Tm_{PAH} = 8 15 ± 2 0

The derived data for plotting the ellipse are

C_{PAH}	Tm_{PAH}	
407	75 9	
415	80 9	72 5
440	86 9	66 .
465	89 4	63.6
490	92 1	61 3
540	95 7	58 7
590	97 9	57 6
610	98 7	57 4
640	99 0	57.6
690	99 0	58 7
740	97 9	60 9
790	95 4	64 5
815	93 3	67 6
840	90 0	70 2
865	84 9	75.7
873	81 2	

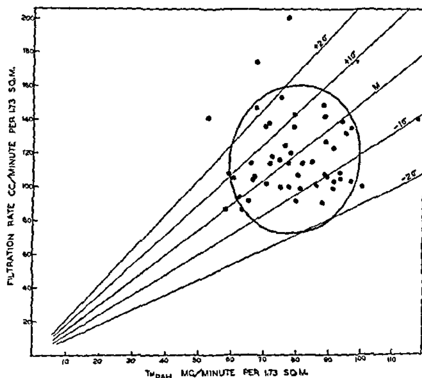


FIGURE 101. The filtration rate in normal man (mixed sexes) as related to Tm_{PAH}. M represents the mean ratio C_F/Tm_{PAH}, ± multiples of the standard deviation. The ellipse is calculated to contain 70 per cent of the observations (corresponding to ±σ) and actually contains 84 per cent.

The 70 per cent ellipse is calculated by the equation given in the text. The basic data used are C_F = 116.5 ± 28.1 and Tm_{PAH} = 79.0 ± 12.9 mg (50 observations), C_F/Tm_{PAH} = 1.5 ± 0.3

The derived data for plotting the ellipse are.

C_F	Tm_{PAH}	
72.8	77.6	
76.5	86.8	68.6
81.0	90.3	65.9
86.5	92.9	63.1
96.5	96.3	60.4
106.5	98.2	59.1
116.5	99.0	59.0
126.5	98.8	59.8
136.5	97.6	61.7
146.5	94.9	65.1
152.0	92.1	67.9
156.5	89.4	71.2
160.1	80.4	

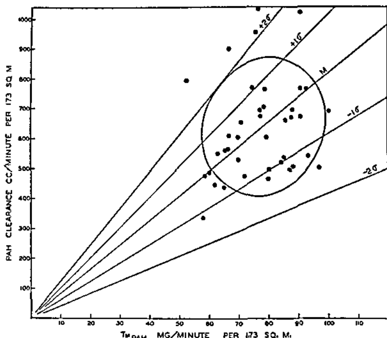


FIGURE 102 The renal plasma flow in normal man (mixed sexes) as related to Tm_{PAH} Again, M represents the mean ratio C_{PAH}/Tm_{PAH}, $\pm$ multiples of the standard deviation The ellipse is calculated to contain 70 per cent of the observations (corresponding to $\pm\sigma$) and actually contains 80 per cent.

The basic data used are $C_{PAH} = 640 \pm 164$ and $Tm_{PAH} = 78.3 \pm 13.4$ (40 observations), $C_{PAH}/Tm_{PAH} = 8.15 \pm 2.0$

The derived data for plotting the ellipse are:

C_{PAH}	Tm_{PAH}	
407	75.9	
415	80.9	72.5
440	86.9	66.7
465	89.4	63.6
490	92.1	61.3
540	95.7	58.7
590	97.9	57.6
610	98.7	57.4
640	99.0	57.6
690	99.0	58.7
740	97.9	60.9
790	95.4	64.5
815	93.3	67.6
840	90.0	70.2
865	84.9	75.7
873	81.2	

of Tm_{PAH} against C_{PAH} in the same patients is 40, of Tm_{PAH} against C_F is 50. The mean Tm_{PAH} in these two series is 78.9 mg., a figure not far different from the average of the means of the sexes treated separately (78.5 mg.) and consequently the figure 78.9 ± 13.2 has been entered in table XII as an appropriate mean for mixed sexes. The values of C_{PAH}/Tm_{PAH} and C_{IN}/Tm_{PAH} entered for the mixed sexes in table XII are the weighted means of the separate sex data.

It is of course to be expected that, as the number of observations on any physiological value increases, the mean and related parameters will shift. However, mere multiplication of the number of observations does not increase the accuracy of these parameters unless all observations are physiologically comparable. Thus the use of single injection methods is apt to lead to erroneously low results for both the filtration rate and renal plasma flow (ch. III), and such data have been excluded from the weighted mean.* These means have been calculated by multiplying each datum by the number of subjects and taking the mean of the whole. Where investigators have not reported the number of subjects studied, their average figure has also been omitted from the weighted mean.

Brun, Hilden, and Raaschou [276] record for 8 males C_{IN}/Tm_{PAH} = 2.01 ± 0.32, C_{IN}/C_{PAH} = 0.206 ± 0.0296, C_{PAH}/Tm_{PAH} = 9.49 ± 0.75, and Tm_{PAH}/Tm_D (mEq.) = 1.77. This last ratio (corrected) in the 10 normal subjects reported by Chasis *et al.*[362] averages 2.51 (range 1.87 to 3.12).

Body weights were not readily available in preparing the data in table XII, but a rough conversion to body weight basis can be made by assuming 60 kg weight in women and 70 kg. in men. Thus calculated, the filtration rate, renal plasma flow, and Tm_{PAH} average 1.81 cc., 9.35 cc., and 1.1. mg., respectively, in men, and 1.97 cc., 10.0 cc., and 1.28 mg. per kg. in women.

Sex Differences

Brun, Hilden, and Raaschou [275] note that in their data there is no sex difference in the diodrast clearance, a probable difference in the filtration rate, and a fairly positive difference in Tm_D. But the weighted av-

* The data of Hogeman on the diodrast clearance are so far out of line with other observations that these data and all derived calculations have also been omitted from the weighted mean.

erages in table XII indicate a significant difference in all three functions when compared on a surface-area basis. Taking the adult kidney weight as 313 gm. in men and 257 gm. in women (*vide infra*) the C_{IN}/KW, C_D/KW, Tm_D/KW, and Tm_{PAH}/KW ratios in men are 0.406, 2.09, 0.16, and 0.247; and in women, 0.46, 2.33, 0.163, and 0.30, suggesting that all functions are slightly higher in women per gm. KW. The data are too few to warrant any firm opinion, however.

The Fraction of the Cardiac Output Delivered to the Kidneys (Renal Fraction)

The renal blood flow is so large that it is a matter of considerable interest to know what fraction this comprises of the total cardiac output in health and disease. Numerous opinions, based on non-simultaneous data, have been expressed. One approach is to divide the average renal blood flow figure recorded by Smith, Goldring, Chasis, Ranges, and Bradley,[1919] of 1209 cc/min. per 1.73 sq. m., by the average cardiac output recorded by Cournand and his co-workers,[439] as determined by the direct Fick method, of 5.29 liter/min. per 1.73 sq. m., which yields the value of 22.9 per cent. Correction of this figure for a 90 per cent extraction of diodrast of PAH from the renal blood would raise the renal fraction to 25.3 per cent. This method of estimation is obviously uncertain, since average figures for renal blood flow and cardiac output vary with the size and composition of the population sample.

Bradley, working in the author's laboratory, endeavored to obtain simultaneous data on a number of subjects, determining the cardiac output by means of the ballistocardiograph; the renal fraction corrected for extraction ratio worked out in the range of 25 to 30 per cent. When it became clear that the ballistocardiographic method was not too reliable for such calculations, this approach was abandoned.

Lauson, Bradley, and Cournand,[1217] in their study of the renal circulation in shock, attempted to establish figures for the normal renal fraction by the simultaneous determination of renal clearances and of cardiac output by the direct Fick method. In 6 subjects they obtained an average value of 16.6 per cent (range 14.4 to 21.2 per cent). Subsequently, Bolomey, Michie, Michie, Breed,

Schreiner, and Lauson[207] completed a series of 18 non-hypertensive and 19 hypertensive subjects, using the direct Fick method. The average cardiac index in the normal subjects was 4.07 liters (or 7.04 liter/min. per 1.73 sq. m.), a figure substantially higher than that of Cournand *et al.* (5.29 liter/min.). The average renal fraction (uncorrected) was 15.6 per cent (range 10.2 to 26.9). However, the multiple procedure of saline infusion, bladder catheterization, and venepuncture for clearance determination, coupled with catheterization of the right heart and the collection of expired gases, is not conducive to physiological quiescence, and it would seem that the inevitable effect would be to increase the cardiac output above the basal level, and possibly to decrease the renal blood flow, thus decreasing the renal fraction. Moderate anemia of some of the subjects in this series may also have led to some reduction in the renal blood flow,[238] and consequently the authors expressed their belief that their figure for the renal fraction might be on the low side.

It is the writer's opinion that a true figure for the renal fraction cannot be determined by these multiple procedures because of the psychological and physiological effects on the subjects, and in the absence of more reliable data he would venture the opinion that the true renal fraction in subjects at rest and with normal hematocrits, and corrected for renal extraction ratios, is between the two figures, namely about 20 per cent.

The data collected by Bolomey *et al.* serve, however, to show that the renal fraction is substantially reduced in hypertensive disease, in consequence of the destruction of renal parenchyma, falling below 10 per cent in many subjects and reaching 1 to 2 per cent terminally.

Senescence

Lewis and Alving[1237] have reported studies on normal men, 20 in each decade from 40 to 89 years, 2 of 91 years, and 1 of 101 years. The whole blood urea clearance declined from 100 per cent of the average normal value (standard clearance = 54 cc., maximal clearance = 75 cc. per 1.73 sq. m.) at 40 years to 55 per cent at 89 years (fig. 103). The urea nitrogen content of the blood increased from 12.03 mg. per cent at 40 years to 17.62 mg. at 89

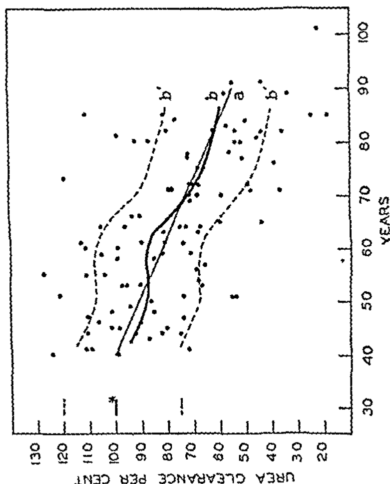
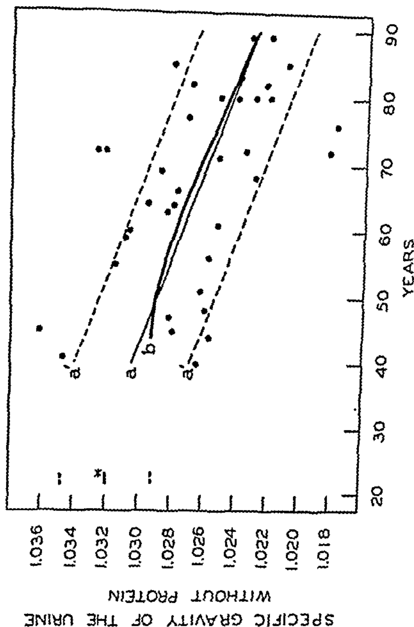


FIGURE 103 Urea clearance in relation to age in normal men over 40 years of age. Dots represent individual values (averages of 2-hr. clearance tests), *a* is the straight line regression, 40 to 89 years, *b* is the smoothed regression of 5-year means, with limits, *b'* (dashed lines), of standard error of estimate, 40 to 89 years, the asterisk represents the average in young normal men, with limits of variation (short dashed lines). (Lewis and Alving [447])



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regression of 10-year means; the asterisk represents the average in young normal individuals, with limits (short dashed lines) of standard deviation. (Lewis and Alving [illegible])

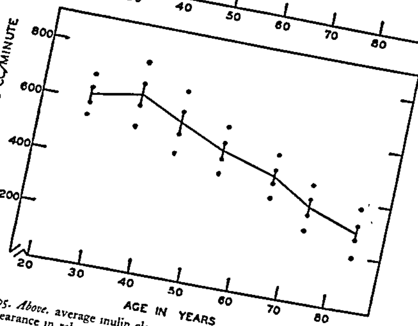
years. The concentrating ability of the kidneys, as shown by the urine specific gravity (corrected for protein) in 38 men after 24 hr. of dehydration, declined from 1.030 at 40 years to 1.023 at 89 years (fig. 104). The specific gravity does not fall below the lower limit of 1.026 observed in younger subjects before the sixty-fifth year, but after this age values in the range 1.023 to 1.026 are more common.

Hilden [1001] gives data on the plasma urea clearance in 8 men 57 to 79 years of age. This clearance ranged from 102 down to 72 per cent of normal and the diodrast clearance from 95 down to 65 per cent. In 8 women 51 to 78 years old, the urea clearance ranged from 90 down to 63 per cent of normal and the diodrast clearance from 84 down to 52 per cent. The urea/diodrast clearance ratio remained at 0.131 in both groups, the same value as obtains in young adults.

Shock [1879] and Davies and Shock [472] report an extensive study of renal function * in 70 males aged 24 to 89 years of age. The subjects were carefully selected to exclude recent or remote renal disease, cerebrovascular accident, coronary artery disease, syphilis, rheumatic heart disease, hypertension, or any recent alteration in body weight. At the higher ages, blood pressure was not considered hypertensive unless the diastolic pressure exceeded 90 mm. Hg, since systolic hypertension with increased pulse pressure may result from dilatation and loss of elasticity in the larger arteries, a change commonly associated with aging. Nevertheless, only 2 tests were done on patients with systolic pressures greater than 160 mm. Hg.

With increasing age there is a progressive diminution in the inulin clearance, diodrast clearance (fig. 105), and Tm_D (fig. 106). Although wide individual differences in the effects of age on renal function are apparent, few subjects in the oldest group gave values as great as those observed in the youngest group.† The regression rates of function on age are given in table XIII.

* The standard error of measurement for the tests made: inulin clearance,



95. *Above*, average inulin clearance in relation to age. *Below:* average
earance in relation to age. (Davies and Shock [11])

TABLE XIII

Regression Rates of Kidney Functions in Adult Men

(Davies and Shock [172])

Y = aX + b, where Y = the function, X = age

Function and units	n *	a † units/yr	b ‡	Regression rate per cent §	r ‖
Glomerular filtration rate, cc/min.	70	−0 96	153 2	0.722	−0.68
Effective renal plasma flow, cc/min	70	−6 44	840 0	0 906	−0 65
Tm_D, mg iodine per min.	70	−0.40	66.7	0 678	−0.66

* Number of cases

† Slope and regression rate of function on age.

‡ Extrapolated value of Y when age is 0

§ Per cent regression per year based on value at age 20.

‖ Coefficient of correlation by product moment formula.

The significances * of the differences between any single adjacent or non-adjacent decades have been summarized in figure 108. Values of the critical ratio as shown in this figure greater than 2.3 are significant at the 5 per cent level.† Examination of this figure shows that the inulin clearance, diodrast clearance, and Tm_D in general show more significant changes between adjacent decades beyond the age of 40 than in early adult life. When alternate decades are examined, the significance of the differences is high for all but young adults; i.e. significant changes occur over 20-year intervals of time.

The filtration fraction, C_{IN}/C_D, does not change significantly between the ages of 20 and 60 (fig. 106). Beyond the age of 60 a small but significant increase occurs. The elevated filtration fraction of the 70 to 79 year group may be owing to sampling errors, since two aberrantly high values occurred in this age category.

* Critical ratios were calculated by the formula:

$$CR = \frac{Mn_1 - Mn_2}{\sigma(Mn_1 - Mn_2)}$$

† Significant at the 5 per cent level means that, if the experiment were repeated a large number of times, a difference as large as (or larger than) this could be expected by chance (where no true difference existed) in 5 per cent of the observations

Both subjects had lower filtration fractions on later tests, but the data from the first test was used to maintain uniformity.

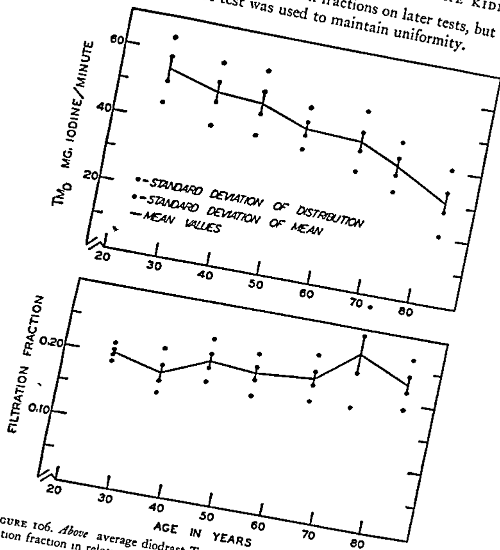


FIGURE 106. *Above* average diodrast Tm in relation to age *Below* average filtration fraction in relation to age. (Davies and Shock [478])

The C_{IN}/Tm_D ratio remains constant between the ages of 20 and 90 * (fig. 107), but the C_D/Tm_D ratio decreases from an aver-

* A critical ratio of 0.3 was found by comparing the average value for 20 to 49 year olds with that of the 70 to 89 year olds

age value of 12.6 at age 30 to 39, to 9 7 at age 80 to 89 (fig. 107). The critical ratio of this difference is 4.2 (P < 1 per cent).

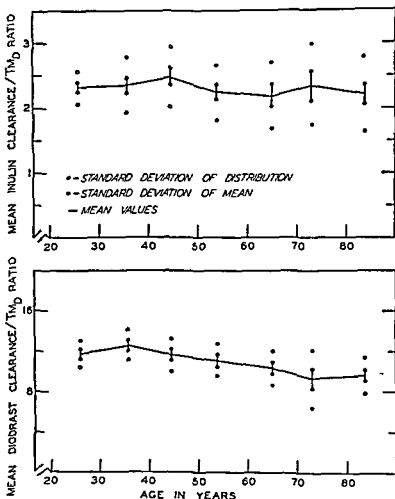


FIGURE 107. *Above* average C_{IN}/Tm_D ratio in relation to age. *Below* average C_D/Tm_D ratio in relation to age (Davies and Shock [473])

The data show that the filtration rate in the men 80 to 90 years of age is approximately half of that in the 20 to 30 year age group. To demonstrate whether or not the mean clearance remains con-

stant between 20 and 40 would require a much larger number of subjects than the present sample. It is safe to say only that there appears to be less difference between mean values of adjacent decades in early adult life than between those of later decades. Although the data presented by Goldring *et al.*[197] are generally higher than the present series when analyzed by age groups, the mean filtration rate of the 50 to 60 year age group is significantly lower than that of the third decade.

Similarly there is a decline in the renal plasma flow in this series, amounting to 53 per cent between the ages of 20 and 90 years. The diodrast clearances reported by Goldring *et al.*[197] are significantly higher than those of the present group in the third decade (critical ratio = 3.55), fifth decade (CR = 2.79), and the sixth decade (CR = 2.41). However, the mean value for the 50 to 59 year group is significantly lower than that for the 20 to 29 year group in the New York subjects as well as in the Baltimore group.

The change in Tm_D (fig. 106) from a mean value of 54.6 mg. of iodine in the 20 to 29 year age group down to 30.8 mg. in the 80 to 89 year group suggests an earlier initial decrease, but subsequently a gentler slope than occurs in renal plasma flow. The differences between the mean values for the two extremes of the age span are highly significant, but somewhat less significant than for analogous decades of inulin and diodrast clearances. For this function a straight line easily fits between the points representing plus or minus 1 standard error of the mean for each decade. Changes in filtration rate and diodrast clearance with age are not so clearly linear. However, with the exception of the 20 to 29 year group in diodrast clearance and the 40 to 49 year age group in inulin clearance, a straight line would fall within a single standard error of the mean of each decade. Although it is improbable that a straight line would represent the true curve reflecting the changes in these functions with age, it is evident that none of them shows a geometric regression.

A marked rise occurs in the filtration fraction of the 70 to 79 year age group over the previous decades. As mentioned above, this may be owing chiefly to the effect of 2 subjects who later returned toward normal, but a slight elevation does occur in the ninth decade. It is safe to assume that a number of subjects in the

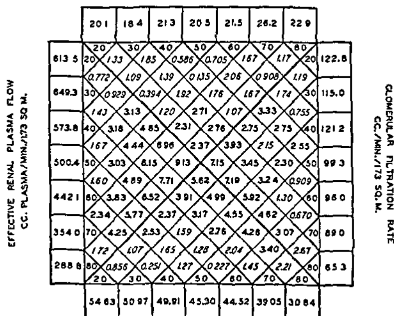


FIGURE 108. Significance of functional differences in relation to age. Average functional values by decades may be found as follows: left-hand vertical column, diodrast clearance; right-hand vertical column, filtration rate, top row, filtra-

face vertical figures.

Example 1. To find significance of the difference between the twenties and forties for diodrast clearance, start at the number 20 in the left-hand margin and follow the column diagonally downward to the intersection with the column

eighties is found by starting at the triangle 30 along the bottom of the figure and following the column upward diagonally to the right until it meets the column rising diagonally to the left from the triangle 80. These columns meet at 4 99 shown in bold-face numbers The difference in diodrast Tm between the 30- and 80-year-old groups is thus significant. (Davies and Shock [471])

ninth decade could be found who have a filtration fraction no higher than that of young adults, but in the general population higher fractions may be most common because of the incidence of hypertension and heart disease. The tendency for the filtration fraction to rise may be due to arteriolar sclerosis.

The constancy of the C_F/Tm_D ratio over 7 decades indicates that the nephron loses its function as a unit and without the formation of aglomerular tubules.

The steady decline in the C_D/Tm_D ratio beyond the fourth decade reveals that the renal tubules of men in the ninth decade are receiving a mean plasma flow of 9.17 cc. per unit of functional tubular tissue, as compared with 12.6 cc. in men in their thirties. This decrease in renal plasma flow with increasing age cannot be attributed to a reduction in cardiac output, since no estimates of cardiac output, crude as they may be, have indicated a reduction of this order of magnitude in elderly subjects.[1236] Nor can it be attributed to decreased mean blood pressure, since this tends to rise slightly with advancing age. It probably reflects progressive vascular changes in the renal parenchyma.

No data are available on renal function in relation to senescence in women. Such data will be awaited with interest.

Davies [472] reports that the urea clearance decreases with age after the fifth decade in a manner parallel to the decrease in filtration rate and Tm_D. Tubular reabsorption declined throughout the 7 decades studied, most of this decline being related to the decreased filtration rate. Urea production does not decrease with age, and hence the blood urea shows a moderate increase. From this preliminary note, one infers that decreased renal function in old age is not related to decreased protein metabolism.

CALCULATION OF BODY SURFACE AREA AND KIDNEY WEIGHT

For inter- or intraspecies comparisons of various animals, it is desirable, as one mode of expression, to use the body surface area. The formula relating surface area to volume

(1)
$$SA = k' \times \text{volume}^{0.66}$$

was developed by Meeh in 1879; if the specific gravity is assumed to be constant, body weight (BW) may be substituted for volume:

(2)
$$SA = k \times BW^{0.66}$$

where SA is in sq. cm and body weight in gm. This relationship subsequently came into widespread use as an approximation equation by Rubner and other students of metabolism The values of k as determined by various investigators for numerous species were collected by Benedict and are reported by Dubois:[548] rat, 9 1; cat, 10.0; rabbit (without ears), 9 0, dog (under 4 kg), 11.2 (over 4 kg.), 10 1; man, 11.0.

Mice: Warren[2143] gives the kidney weight in male mice 35 to 195 days of age as 15 2 mg/gm, in females 12.9 mg/gm.

Rat Lee[1222] prefers the use of the exponent $BW^{0.60}$ and a value of k = 12 54 over previously published data. (A formula using a nutritional factor is somewhat more accurate.)

The writer calculates the KW/BW ratio in Wistar rats 50 days of age or older in Arataki's[55] data to be 8.04 gm/kg. in males and 8 08 gm/kg in females. Dicker[513] obtained a KW/BW ratio of 7 5 to 8 8 gm/kg depending on the protein content of the diet Taking this ratio as 8.0 and using Lee's formula, a 200 gm. rat would have 130 gm. of kidney per sq m.

In view of some apparent differences in function in different strains, it is of interest that in the older Wistar strain[536] KW = 0.00718 (BW_{gm} − 3) + 0 132 log (BW_{gm} − 3) − 0 009 for male rats, which yields for a 300 gm. rat about 8.3 gm/kg This ratio in rats 110 days old or more in the data of MacKay and MacKay[1337] in decapsulated, sectioned, and blotted kidneys is 5 44 gm/kg in males and 5 68 gm/kg. in females, figures not to be compared with those of other investigators who did not decapsulate the kidney but only freed the capsule of fat. The data of MacKay and MacKay show that adult male rats have 35.6 gm, females 31 0 gm, of decapsulated blotted kidney per sq. m The right kidney is a trifle heavier than the left in both sexes[55,1340]

Kirkman and Stowell[1121] estimated the total filtration surface in the male albino rat to be 11,704 sq. mm (6890 sq. mm. per gm of kidney) and from available data inferred that the urea clearance in the rat and man (using Book's estimate of filtration surface in the latter) agree within 18 per cent in terms of kidney weight, and 0.2 per cent in terms of surface area.

Cat: No formula is known to the writer which improves on the Meeh-Rubner equation.

Hall and MacGregor[859] give the formula for kidney weight as

$$(3) \qquad KW_{gm} = 9.825 \times BW_{gm}^{0.71} - 1.09$$

or with almost as much accuracy for medium-sized animals,

$$(4) \qquad KW_{gm} = k \times BW_{kg}.$$

For males weighing 3.0 to 3.5 kg, k = 9.4; for females weighing 2.5 to 3.0 kg, k = 7.2. The markedly larger figure in male cats should be noted. In old males the figure is still larger (10.2).

Rabbit: Kaplan and Smith [1090] calculated from the data of Taylor, Drury, and Addis [2049] on 17 rabbits that

(5) $$KW = 8.9 \times BW_{gm}^{\;0.66}$$

The figure is probably valid only between 2 and 4 kg. From these same data the writer obtains the relationship:

(6) $$KW_{gm} = 6.4 \times BW_{kg}$$

(7) $$KW_{gm} = 89 \text{ gm/sq. m.}$$

while W. W. Smith [1947] gives for 8 rabbits

(8) $$KW_{gm} = 5.6 \times BW_{kg}$$

Dog Cowgill and Drabkin [442] made a careful study of the dog, and presented a nomogram which is superior to the Meeh-Rubner formula and which is almost universally used. As an equation they recommend

(9) $$SA_{sq\ cm} = 2.268 \times BW_{gm}^{\;0.367} L_{cm}$$

where L is the length from nose to anus measured over the belly.

Stewart's [2005] data on 5 dogs (5 to 18 kg), in which he measured the surface area, yield the relation, according to Cowgill and Drabkin,

(10) $$SA_{cm} = 6.63\, BW_{gm}^{\;0.71}$$

and Thomas' data on 6 dogs yield

(11) $$SA_{cm} = 7.48\, BW_{gm}^{\;0.71}$$

Graphical analysis of Kunkel's data for 13 dogs (5.2 to 20.0 kg) indicates the relationship

(12) $$SA_{cm} = 11\, BW_{gm}^{\;0.66}$$

though K might well be 10.

Stewart gives the KW/BW ratio as 7.2 gm/kg for 8 dogs below 8 kg, and 3.4 for 4 dogs above this weight. In his larger series (table 4) this ratio was 7.2 below 10 kg. and 5.8 above. Calculation * from Stewart's larger series shows that, in 16 dogs weighing from 7 to 18 kg., the KW/BW ratio is 6.28 gm/kg. In Kunkel's [1117] 9 dogs, weighing from 5 30

* The writer is indebted to Mr. Charles Crowder, Jr, for these and other calculations.

to 20.00 kg., KW/BW = 7.3 gm/kg. Moustgaard's [1453] series of 88 dogs in the weight range of 5 to 10 kg , 10 to 15 kg., 15 to 20 kg., 20 to 25 kg , [illegible] KW/BW [illegible] and

[illegible]

data It is probable that differences in diet as well as differences in preparing the kidneys for weighing may play a part in giving rise to this discrepancy.* The best figure based on the above data appears to be

(13) $$KW_{gm} = 7.1\ BW_{kg}$$

Dividing (12) by (13) yields 141 gm/sq. m , a figure in fair agreement with (16) below

Several calculations are possible on a surface-area basis. (a) Stewart's data for 5 dogs between 5 and 18 kg. give 105 gm/sq. m. as measured. (b) Calculation of surface area by (12) yields, for 15 dogs weighing from 5 to 19 kg , 131 gm/sq. m. (69.9 to 176 6). (c) Kunkel's data [1117] on 9 [illegible]

[illegible]

an average value of 100 gm/sq m ; (e) the surface area as calculated by (9) on 88 dogs yields 135 gm/sq m.; (f) if surface area is calculated by (12) these 88 dogs yield 110 gm/sq. m (g) Moustgaard, from data on 88 dogs, arrives at the relation

(14) $$KW_{gm} = 0\ 15BW_{kg}^{0\ 63}\ L_{cm}$$

Dividing this equation by (9) we obtain

(15) $$KW_{gm/sq\ m} = 8\ 53\ BW_{gm}^{0\ 263}$$

If we divide (15) by (12) the resulting expression

(16) $$KW_{gm/sq\ m} = 3.4\ SA_{sq\ m}^{0\ 395}$$

yields 129 gm for 1 sq m The correspondence between this figure and those obtained by calculations (b), (c), and (e) is remarkably good, and we take the kidney weight in the dog to be about 130 *gm/sq m*. Sex was not specified in any instance

Man: Dubois [548] has presented the widely used nomograms relating surface area to height and weight in adults and children. As a rough [illegible]

approximation he recommends k = 10.79 in the Meeh-Rubner formula for adults and 10.3 for children. The Meeh-Rubner formula is close enough for general purposes, but slightly more accurately in adults is

$$(17) \qquad SA = BW_{gm}^{0.425} H^{0.725} 71.84$$

Surface area in infants is given by Klein and Scammon[1128] as 5.188 $BW_{gm}^{0.75}$

MacKay[1325] calculates from the data of Vierordt[2112] that man has 171 gm. of kidney per sq. m., but does not say whether he used the data on males, females, or both, and in the calculation he used average data from two independent series on body height and weight. The writer has recalculated Vierordt's data for the age groups 20 to 25 years, multiplying the number of observations by the renal weight in each group, and obtained an average of 302 gm in men and 276 gm. in women. Greenwood and Brown[857] give the average weight of the kidney in healthy males 25 to 55 years of age as 303 gm. ($\sigma/m = 0.1921$). (The same sources may have been used in these two series.) In Wald's[2124] data on subjects dying within 24 hr. of accident, with no history of illness or pathologic abnormality, at 20 to 29 years the average kidney weight in males is 313 ± 59.0, at 30 to 39 years 323 ± 57.0, at 40 to 49 years 316 ± 54.4 gm., while in females the corresponding figures are 257 ± 54.5, 250 ± 47.6, and 258 ± 52.8 gm. Taking all age groups in Wald's data, the weight of the kidney in women averages 82 per cent of that in men. For present purposes we shall take Wald's figures of the second decade (313 for men and 257 for women) as applying to 1.73 sq. m.; using 70 and 60 kg. respectively, these would give 4.47 and 4.29 gm/kg.

Lattimer reports the kidney weight in men to be 6.68, in women 5.99 gm/kg. between the ages of 20 and 40 years In infants these figures are 10.2 in males and 9.90 in females All these coefficients appear to be high and may represent emaciated individuals.

GLOMERULAR COUNTS

It is of interest to relate the basal function in the rat, rabbit, dog, and man to the glomerular and tubular development of the kidney. This can only be accomplished by combining the data of various investigators. The number of glomeruli in one kidney of the adult animal (the number of animals is shown in parentheses) is recorded as follows (the number of glomeruli in the adults of all species studied remains fixed, and there will therefore be no correlation between number of glomeruli and body size within species):

Rat: 28,000 (3);[1126] 31,000 (12);[65] 33,826 (1);[2114] 30,750 (2);[1177] 25,300 (4);[2058] 30,800 (8).[1761] Kunkel[1177] from his data on 2 rats estimated an average of 2,118,000 glomeruli per sq. m., or 27,000 per gm. KW. Arataki's[65] 6 males 100 days or more of age give 27,000, and 6 females give 35,100.

Vimtrup's count[2114] on 1 rat gave 32,200 glomeruli per gm KW. The weighted mean of these figures gives 30,600 per gm. KW.

The total number of glomeruli in the white rat decreases by about 30 per cent in senile animals.[66, 1474]

Rabbit 212,269 (10);[1501] 202,850 (2);[1177] 207,000 (?).[1761] Hayman and Starr's[942] maximal figures range about 200,000. Kunkel found 2,030,000 per sq. m. in 2 animals. For a 2 kg. rabbit, Nelson's figure and k = 9.0 would give 1,490,000 per sq. m. For a 2.0 kg. rabbit, equation 5 gives 6.4 gm. for one kidney, and the mean of the figures above gives 33,300 glomeruli per gm. KW. (Kunkel obtained 33,000 in 1 rabbit with a 6.5 gm. KW.)

Cat: 182,600 (3),[2114] 199,300 (?).[1761] Vimtrup obtained 15,200 glomeruli per gm. KW, Kunkel 9,000 (male with large kidney?) and 23,000 (female?).

Dog. Kunkel determined the number of glomeruli in one kidney in 14 dogs to be 426,000; Rytand[1761] obtained 408,100 in 1 dog (9.1 kg.), and Vimtrup[2114] 457,500 in 2 dogs. Kunkel calculates for 14 dogs (both kidneys) 1,920,000 glomeruli per sq. m. (as measured), or 117,000 per kg. body weight; in 9 Kunkel obtained 13,350 glomeruli per gm. KW; Vimtrup 13,700 in 2 dogs.

Man. 1,040,000 or 7,170 per gm. KW (1);[1126] 955,434 (range 833,992 to 1,233,360) (5).[2114] The writer has excluded from Moore's[1473] series 2 cases of miliary tuberculosis and 1 of rheumatic heart disease, leaving 14 kidneys from patients 1 to 38 years old; the average is 874,448 (range 651,596 to 1,040,671). Moore's data indicate that the glomerular count decreases by one-third to one-half by the seventh decade.* Vimtrup's[2114] figures on 2 human kidneys (sex unspecified) give 6,060 and 7,470 glomeruli per gm. KW. The best figure appears to be about 7000 per gm. KW, or 2,190,000 in man and 1,800,000 in women, assuming that the

* Moore gives the number of glomeruli per gm. of cortex, but the counts were made on individuals dying of diseases many or some of which were severely wasting (chronic tuberculosis, lobar pneumonia), and the kidneys had been perfused with fresh water and were edematous. These figures, however, averaged 15,839 in 7 women and 11,009 in 15 men. In the 7 women the total glomerular count averaged 793,038 per kidney, and 763,264 in the men. The data suggest that the female kidney has the same number of nephrons as the male kidney but each nephron is smaller, accounting for the smaller kidney weight.

TABLE XIV

Comparison of Renal Function in Mammals

(Sources of data are discussed in the text.)

	KW/sq. m.	Glomeruli per gm. KW	Per glomerulus × 100,000			Per gm. KW			Per kg. BW			Per 1.73 sq. m.		
			C_{IN} cc.	C_{PAH} cc.	Tm_{PAH} mg.	C_{IN} cc.	C_{PAH} cc.	Tm_{PAH} mg.	C_{IN} cc.	C_{PAH} cc.	Tm_{PAH} mg.	C_{IN} cc.	C_{PAH} cc.	Tm_{PAH} mg.
Rat	130	30,600	2.45	8.99	1.22	0.75	2.75	0.375	6.00	22.0	3.0	69.9	253	34.6
Rabbit	89	33,300	1.98	7.50		0.66	2.50		3.12	18.2		87.0	512	
Dog	130	13,350	4.64	14.3	1.03	0.62	1.91	0.137	4.29	13.5	0.97	146	460	33.0
Man *	149	7,000	6.56	33.3	4.29	0.46	2.33	0.300	1.97	10.0	1.28	118	600	77.2

* Women, for comparison with female dogs.

difference in renal weight is entirely referable to a difference in the number of nephrons.

Moore[1471] records that the number of glomeruli in the human kidney decreases with age; in the seventh decade it is one-third to one-half the number in young adult men.

Data from the calculations above have been brought together in table XIV to afford a comparison of renal function in different species. These data indicate that, per unit of body surface area, the rat, the dog, and man have about the same quantity of renal tissue. But man has the smallest number of nephrons (glomeruli), so that each nephron must have more tubular tissue attached to it, an inference confirmed by the higher value of Tm_{PAH} per nephron. The filtration rate per glomerulus in man is also higher than in the rat, and possibly than in the dog. These differences almost entirely cancel out when comparison is made on the basis of kidney weight.* In all species, each gm. of kidney makes about the same quantity of filtrate and has about the same value of Tm_{PAH}. Per unit of body weight, renal function is higher in small animals, a fact which may be related to the circumstance that metabolism is greater per unit of body weight in small than in large animals. These differences are reduced, if not abolished, when total function is compared on a surface-area basis, reflecting the applicability of the surface-area law to metabolism. The difference between the last methods of calculation in favor of the surface-area basis lends further warrant to this method of comparison within a species and as between young and adult animals.

Kunkel[1177] gives data on the number of glomeruli in the monkey, opossum, ground hog, pig, ox, cat, rabbit, rat, mouse, and guinea pig. The number of glomeruli in his series correlated more closely with body surface area than with body weight.

Rytand[1761] gives glomerular counts on 1 elephant and 4 to 8 male mice, albino rats, and kangaroo rats, and measurements of the unfixed glomeruli suspended in serum. Combining his data with those of Kunkel, he calculates the total glomerular volume (TGV) and relates it to kidney weight and body weight, as shown in table XV.

He finds that TGV is almost a linear function of the kidney weight, as shown by the constancy of the ratio of the two in table XV; hence

$$TGV_{cu\ mm} = 0.044\ KW_{mg.}^{1.0} \tag{18}$$

Rytand apparently drew his curve by visual fit and included the ele-

* It has been noted above that, relative to man, the dog is deficient in respect to Tm_{PAH} (as judged per unit of filtrate) but not deficient in respect to Tm_{D}.

TABLE XV

Body Weight, Kidney Weight, Glomerular Size, and Glomerular Number in Several Mammalian Species

The data for the mouse, albino and kangaroo rats, and elephant are Rytand's.[1761] The data for man are taken from the text, and data for other species were recalculated by Rytand from Kunkel.[1117]

Animal	Body weight	Weight of one kidney	Glomerular radius	Number of glomeruli in one kidney	Total glomerular volume in one kidney	Total glomerular volume in 1 gm. of kidney
	gm.	mg	μ		cu mm	cu mm.
Mouse	20	123	36.7	12,430	2.6	21.1
Kangaroo rat	66	295	48.4	18,840	8.9	30.3
Albino rat	241	746	61.2	30,800	29.5	39.5
Guinea pig	565	1,900	63	75,700	79.3	41.7
Ground hog	1,210	1,800	69.5	96,000	135	75
Opossum	2,000	5,200	87.5	91,200	256	49.2
Rabbit	2,320		71	207,000	310	
Cat	2,750	8,000	66	184,000	227	28.3
	3,500	25,500	75	214,500	379	14.9
Monkey	3,860	9,000	83	186,600	447	49.7
Dog	9,100	31,300	90	408,100	1,247	39.9
Pig	46,650	76,700	83	1,193,000	2,859	37.3
Man	70,000	156,500		1,095,000	4,599	29.4
Ox	410,000	640,000	122	3,992,000	29,860	46.7
Elephant	4,545,000	3,650,000	169	7,510,000	151,900	41.6

phant and excluded the mouse (fig. 109). The writer has calculated the regression line, omitting the elephant and including the mouse, and obtains practically the same slope but a slightly smaller constant:

$$TGV_{cu\ mm} = 0.0296\ KW^{1.024} \quad (19)$$

The elephant remains in line with this equation (fig 109).

The exponent is so close to 1.0 that it is approximately correct to say, with Rytand, that on the average there are 30 cu. mm. of glomerular volume (eq. 20) in each gm. of kidney. The cat is way out of line, probably because of large tubules. Using Vimtrup's[2116] figure for the average glomerular volume in man of 0.0042 cu. mm., 7000 glomeruli per gm would give 29.4 cu. mm per gm.—an agreement with Rytand's generalization that is too good to be true.

Rytand also derives the following relations (N is the number of glomeruli) for 1 kidney:

$$N = 508\ KW_{mg}^{\ 0.65} \quad (20)$$

(21) $$KW_{mg} = 8.22\, BW_{gm}^{0.85}$$

(22) $$TGV_{cu\ mm} = 0.36\, BW_{gm}^{0.85}$$

Recalculation of (22), omitting the elephant and including the mouse as in figure 109, gives

(23) $$TGV = 0.1987\, BW_{gm}^{0.9287}$$

All these relations * are probably approximate only. Equation 22 would yield for a 70 kg man 250 gm. total kidney weight, which would be about right for women.

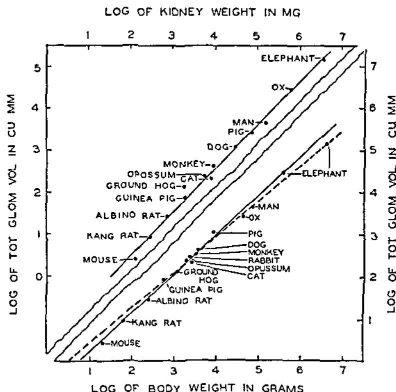


FIGURE 109 Total glomerular volume in relation to kidney weight (above) and body weight (below) in mammals. The data on man are calculated in the text (Rytand [1761])

* The fact that the exponent in the last three equations is less than 1.0 indicates lack of simple proportionality. It should be noted, however, that a log-

Rytand's inference that TGV, which he finds is fairly constant per gm. of kidney, should be closely proportional to glomerular function, is supported by the constancy of the filtration rate per gm. of kidney, as shown in table XIV.

COMPARISON OF LOWER AND HIGHER VERTEBRATES

In closing this chapter, it will be of interest to the student of comparative physiology to compare renal function in the mesonephros and metanephros, particularly with reference to the relative importance of glomerular and tubular activity.

It will be recalled that, in Pisces, Amphibia, Reptilia, and Aves, the definitive kidney, or mesonephros, receives a copious supply of blood from the veins of the posterior part of the body, this venous blood perfusing the tubules and mingling with the postglomerular blood in the venous channels draining the kidneys (ch. 1). Unfortunately no functional data are available on the fresh-water fishes, where the arterial-glomerular circulation could be expected to dominate over the renal-portal circulation.

Nash[1600b] has shown that total glomerular volume is much larger per unit of surface area in fresh-water teleosts than in marine forms, the marine elasmobranchs and cyclostomes resembling the former.

It may be surmised that under conditions of threatened dehydration, such as would be faced by the anadromous salmon or catadromous eel during the marine phase, glomerular activity is reduced to low levels in order to conserve water It is, however, doubtful that glomerular activity ceases entirely, since it does not do so in most permanently marine forms, and the development of the aglomerular state in old sculpin must be looked upon as a developmental phenomenon related to biological degeneration rather than atrophy in the individual from lack of function. But comparison of urine flow in the salt- and fresh-water elasmobranchs, as noted earlier in this chapter, indicates that such an adjustment occurs in this Sub-class.

Glomerular function can be evaluated by the filtration rate, C_F, and tubular function by phenol red Tm, the only substance which has been studied in the lower vertebrates. Of equal importance is the rate of perfusion of the tubules, since this would comprise both the renal blood flow through both the postglomerular and renal-portal circulation. For such comparisons, we have calculated the tubular perfusion, C_T, from

log relationship is precarious, for almost any 2 progressive variables will yield an approximately linear relationship when so treated, large absolute deviations showing up as only small departures from the apparent logarithmic relationship.

data on the phenol red clearance, corrected for an extraction ratio of 0 50 (an assumed and doubtless inaccurate value). Since so little phenol red is excreted by filtration, neglect of this term introduces no significant error.

The data in table XVI show that glomerular clearance is, of course, zero in the aglomerular toadfish and goosefish. In the glomerular dogfish (marine) the filtration rate is very low, the ratio C_T/C_{IN} very high. In the fresh-water bullfrog, the filtration rate is better than 10 times as great as it is in the marine dogfish, probably reflecting differences in hydration rather than in glomerular development, for the glomeruli are

TABLE XVI

The Excretion of Inulin and Phenol Red in Various Vertebrates, Showing the Relative Importance of Glomerular and Tubular Function

	C_F cc/min per kg	C_T cc/min. per kg.	C_T/C_{IN}	Tm_{PR} mg/day per kg.	Tm_{PR} mg/100 cc. of filtrate
Cold blooded, Mesonephros					
Toadfish *	0	1	∞	13 6	∞
Goosefish *	0	1	∞	9 3	∞
Dogfish † (salt water)	*0 05*	*2 25*	*45*	*18 0*	*25*
Frog ‡ (fresh water)	0 66	11 6	16 0	120 0	12 6
Warm-blooded, Mesonephros					
Chicken §	1 84	50 0	26.0	1643 0	62
Warm-blooded, Metanephros					
Rat ‖	6 0	22 0	3.7		
Rabbit ‖	3 12	18 2	5.8		
Dog ‖¶	4 29	13 5	3 1	495	8
Man ‖**	1 97	10 0	5 0	288	10

* C_T at best a rough guess, estimated from Shannon's[1857] figures, assuming E_{PR} = 0 5, other data from same source

† C_{IN} from Shannon[1844] and W W Smith,[1945] C_T from W W Smith taking E_{PR} = 0 5, Tm_{PR} from same source

‡ C_{IN} from Forster[677] on summer frogs C_D from same source, taking E_D = 1 0, Tm_{PR} from Forster[675] In Forster's earlier paper[674] he gives the inulin clearance in winter frogs as 0 33 cc/min per kg during maximal water diuresis

§ C_{IN} and C_{PR} from Pitts[1628] taking E_{PR} as 0 5, Tm_{PR} from the same source

‖ Data from table XIV, taking E_{PAH} as 1 0

¶ Tm_{PR} from Shannon[1847]

** Tm_{PR} in one subject only, from Smith, Goldring, and Chasis[1938]

well developed in the latter. Tubular perfusion is, however, increased fivefold, possibly because of an abundant postglomerular flow. Tm_{PR} per kg. of body weight is increased many times; discounting differences in temperature (dogfish 15° C.?, frog 20° C.?), this increase implies either a greater quantity of proximal tubular tissue in the frog or greater specific excretory activity. Despite the increase in Tm_{PR}, the ratio Tm_{PR} per 100 cc. of filtrate is reduced as compared with the dogfish. In the frog, glomerular activity is relatively more important than tubular activity.

Although the chicken has a mesonephros, the appearance of the warm-blooded state may account for the remarkable increase in tubular activity. But if Q_{10} = 2 0 per cent (and it may be greater), a difference in temperature of 15 to 39° C. would only account for a 2.5-fold increase, whereas the actual increase as compared with the frog is nearly fourteenfold. The increase is less in the filtration rate, a fact which is not surprising, since filtration is not temperature-sensitive, but one which may in part be attributed to poor glomerular development. Pitts [1823] gives the kidney weight in 2 chickens as 7.15 gm/kg.; this conversion would give a filtration rate of 0.258 cc/gm. KW, a figure to be compared with 0 46 cc. in women and 0.405 cc. in men. It is surprising, in view of the structure of the glomerulus in the chicken, that this figure is so high. The ratio C_T/C_{IN} remains high, showing that tubular perfusion through the renal-portal system accounts for most of the renal blood flow.

For comparison, the data from mammals are reproduced from table XIV. As noted above, glomerular activity is greater in mammals than in the chicken because of better vascularization of the glomeruli With the disappearance of the renal-portal system, the ratio C_T/C_F falls to a level substantially below that observed in the mesonephric forms, and tubular activity, as judged by Tm_{PR} per 100 cc. of filtrate, decreases to a value below that of the frog.

The data, meager as they are, support the interpretation that, with the evolution of warm-blooded forms capable, unlike the bird, of elaborating a hypertonic urine, glomerular activity was preserved and played [illegible] by an extravagant process of [illegible] ively less im- [illegible] fostered the disappearance of the renal-portal system, or whether the disappearance of the renal-portal system fostered the increased emphasis on filtration, remains as yet, like so many problems in evolution, an enigma within the story of adaptation and natural selection.

CHAPTER XVIII

Renal Hemodynamics *

THE NATURE OF GLOMERULAR FILTRATION

Any approach to the problem of renal hemodynamics must start from certain premises concerning the nature of the processes of capillary transudation in the kidney. The view accepted by Cushny, which was based upon the contemporary views of Starling and which is the one now accepted by all investigators, is that the separation of the glomerular filtrate is the result of a simple process of ultrafiltration of water and its contained solutes (other than the plasma proteins, lipids, and other macromolecules) through the capillary tuft, the effective filtration pressure being the difference between the hydrostatic pressure within the capillaries on the one hand and the sum of the oncotic pressure plus the hydrostatic pressure in the capsule on the other. This view requires that the glomerular membranes be permeable to all plasma electrolytes and other substances possessing significant osmotic pressure, for otherwise their osmotic pressure would render filtration impossible. The total osmotic pressure of the plasma may be taken as $-0.553/1.85°$ C $\times 22.4 \times 760$ mm. Hg, or 5090 mm. Hg, whereas the pressure in the glomerulus available for filtration does not exceed 60 mm.

* This chapter has been prepared with the assistance of Dr Domingo M. Gomez A more detailed exposition will be presented elsewhere

In many though not all instances, changes in the renal circulation leave the filtration rate essentially unchanged despite wide variations in renal blood flow. This constancy of the filtration rate (under these particular conditions) might be construed as evidence that the properties of the glomerular membranes are such that the rate of filtration is independent of glomerular pressure, a hypothesis wholly contrary to the concept of simple ultrafiltration. We have no direct knowledge of the rate of passage of water *per se* across the glomerular membranes, the filtration rate being defined in terms of reference substances such as inulin or creatinine. It might be argued that the constancy of the inulin clearance issues from the circumstance that the glomerular membranes so condition the passage of inulin molecules that the quantity which enters Bowman's capsule per unit time is constant and independent of the passage of water. This supposition is controverted by the facts, first, that inulin is present in the capsular fluid of the frog and *Necturus* in the same concentration as it is present in plasma water; and, second, that under controlled conditions in all species examined inulin is always excreted in proportion to the plasma concentration. There is no limiting rate of glomerular excretion of inulin (as in tubular excretion) and the fact that its excretion is so strictly dependent on plasma concentration requires the simultaneous passage of water in equivalent amounts. When to this evidence there is added the similar evidence on the simultaneous excretion of creatinine in the dog, rabbit, etc., it may be said that the data require the simultaneous passage of water and inulin (or creatinine) in the proportion in which they exist in the plasma.

It could still be argued, however, that the glomerular membranes are so constructed as to permit the passage into Bowman's capsule per unit time of a constant volume of water with its contained inulin and all other solutes, the volume so passed being relatively independent of glomerular pressure. (Such a system is roughly imitated in a 'slow' filter, i.e. one in which the resistance is so high that the movement of fluid is but slightly influenced by moderate changes in hydrostatic pressure.) Any membrane thus conditioning the passage of water independently of pressure can do so only by being relatively impermeable, and its properties must be such that the movement of water is conditioned by inter-

molecular forces such as solubility in heterogeneous phases, surface tension, adsorption, diffusion, etc., or cellular transport involving such forces (secretion), and under these circumstances it can confidently be expected that the passage of various molecular species will be differentially conditioned. The now abundant evidence on the excretion of inulin, creatinine, and a variety of other substances presents no evidence of such differential permeability.

If the positive evidence is adequate to exclude the conditioned passage of inulin specifically, and the conditioned passage of water and solutes generally, then the only alternative is to accept the hypothesis that water with its contained solutes moves through the glomerular membranes in consequence of differences in hydrostatic pressure, not restrained to a significant degree by viscous or frictional forces. This is, of course, the Starling concept of ultrafiltration and the accepted concept of glomerular filtration.

FILTRATION PRESSURE EQUILIBRIUM

The passage of water with its diffusible solutes into Bowman's capsule occurs only in consequence of the fact that the hydrostatic pressure within the glomerular capillaries exceeds the sum of the oncotic pressure plus the capsular pressure. By capsular pressure we designate the pressure existing in Bowman's capsule; it may be accepted that the compressibility of this capsule is such that the capsular pressure is practically identical with the renal interstitial pressure.*

In conformity with the principle of ultrafiltration, we conceive the filtration process to be a reversible one, so that, if the pressure in the glomerular capillaries falls below the sum of the oncotic plus capsular pressure, filtration will be reversed and fluid will be reabsorbed from the capsule into the glomerular capillaries.†

* This generalization, however useful or even necessary in the present discussion, should not be taken to mean that the interstitial pressure is the same everywhere throughout the kidney Gottschalk (pers com) has shown that the injection of saline into one pole of the kidney in sufficient quantity to produce a bleb and a considerable local increase in pressure does not immediately increase the interstitial pressure at the other pole. The kidney as a whole does not behave like a completely fluid system.

† A minimal filtration (isogravimetric) pressure about equal to the oncotic pressure is demonstrable in muscle[1474]

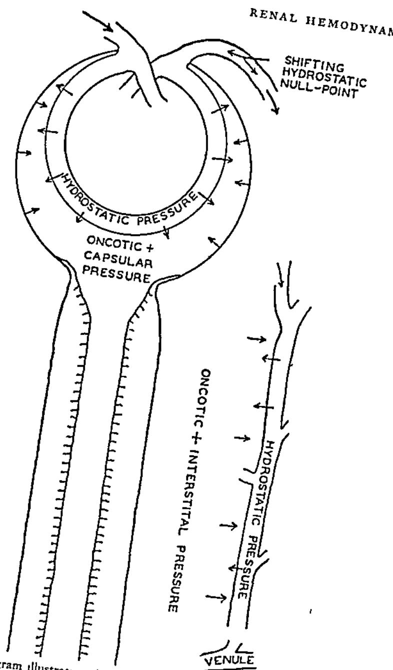


FIGURE 110. Diagram illustrating the hemodynamic factors involved in filtration and reabsorption.

Also in accordance with the principle of ultrafiltration, we conceive that it is because hydrostatic pressure is less than the sum of the oncotic plus interstitial pressure that fluid is reabsorbed from the interstitial space into the peritubular capillaries.

As the blood traverses the glomerular capillaries, the oncotic pressure will rise in consequence of increasing concentration of protein. Similarly, the oncotic pressure will decrease in the peritubular capillaries during fluid reabsorption (fig. 110). Should the opposing pressures tending to effect filtration and reabsorption become equal to each other in either of these capillary beds, transfer of fluid across the membrane would cease and filtration equilibrium would exist. Considerably doubt exists that filtration equilibrium is reached in either the glomerular or peritubular capillaries, but it will be very closely approached in the latter, despite the transfer of a large volume of reabsorbate, because of the large permeability coefficient. From a teleological point of view it is doubtful that filtration equilibrium occurs in the glomeruli, for this would waste the latter portion of the capillary plexus from filtration and, by promoting reabsorption of fluid, would in some measure defeat the filtration process. Again, teleologically, it is doubtful that it would occur in the peritubular capillaries, for this would waste the early portion of these capillaries from reabsorption and, by promoting filtration, would in some measure defeat the reabsorptive process Ideally, the hydrostatic null point or point of equality between opposing pressures should occur in the proximal end of the efferent arteriole with continued fall in pressure distally, thus promoting maximal filtration in the glomeruli and maximal reabsorption in the peritubular capillaries.

FILTRATION PRESSURE

The hydrostatic pressure in the mammalian glomerulus cannot be calculated directly Winton's studies [2243] on the isolated dog kidney indicate that the mean glomerular pressure in this preparation can vary from 30 to 90 per cent and averages about 60 per cent of the mean arterial pressure. Selkurt, Hall, and Spencer [1823] have found that the renal plasma flow and filtration rate are well maintained in anesthetized (pentobarbital) dogs at arterial pressures ranging from 150 down to 100 mm. Hg at lower

both functions decrease, the filtration rate decreasing more rapidly than the renal plasma flow, leading to a marked decrease in filtration fraction. Urine flow ceases at a pressure of about 60 mm. Hg, indicating that filtration stops at this arterial pressure. Because of decrement of pressure in the afferent arterioles, this figure throws no light on the minimal filtration pressure itself except to indicate that it may be of the order of 60 per cent of 60 mm. Hg or 36 mm. Hg, i.e. somewhat above the oncotic pressure of the plasma (25 mm. Hg), as would be required in theory since some pressure head is required to effect filtration and move fluid down the tubules.

INTERSTITIAL (OR INTRARENAL) PRESSURE

Winton [2248] indirectly estimated the intrarenal pressure in the isolated perfused dog kidney by measurements of the arterial and venous pressures and the ureteral pressure in relation to changes in urine flow, and obtained an average figure of 10 mm. Hg. During some types of diuresis the pressure rose to 20 to 30 mm. Hg. A question may be raised, however, about the applicability of this indirect method, and especially with respect to the use of ureteral rather than pelvic pressures in such calculations.

Gottschalk (pers. com.), using capillary pipettes of approximately 100 μ diameter and noting the pressure required to cause minimal and reversible movement of fluid into the interstitium, btained an average interstitial pressure of 10 mm. Hg in cats, bbits, guinea pigs, and rats. When venous pressure was ineased by progressive compression of the renal vein, the intertial pressure remained constant until the renal venous pressure roached the pre-existing intrarenal pressure and then began to . At renal venous pressures above 20 mm. Hg the interstitial sure was at most 1 or 2 mm. more than the renal venous pres- Reducing renal arterial pressure by compression of the abal aorta had no consistent effect on interstitial pressure at l pressures of 40 to 120 mm. Hg; below 40 mm., interstitial e began to decrease. Death of the animal, or complete of the renal artery, reduced the interstitial pressure and

the renal venous pressure to the same level, i.e. to 1 to 3 mm. Hg.*

Ferris (pers. com.), in observations made by means of a capillary pipette and a 25 gauge needle with side perforations, obtained values of 14 and 18 mm. Hg in 2 subjects without evidence of renal impairment, and undetermined values greater than 45 mm. Hg in 2 subjects with acute mercury nephrosis and anuria with visual evidence of renal edema Since the renal venous pressure in man averages 11.5 mm. Hg,[1419] it seems reasonable and convenient, for hemodynamic calculations in the normal subject, to take the intrarenal pressure as 10 mm Hg. Where the renal interstitial pressure is increased by an increase in renal venous pressure (cardiac failure, etc) on the basis of Gottschalk's observations it may be taken as equal to the latter. Where renal edema is present the interstitial pressure may be substantially higher than the renal venous pressure and no quantitative statements can be made in advance of measurement.

RENAL VENOUS PRESSURE

Blake, Wegria, Keating, and Ward report that the normal renal venous pressure in the anesthetized (pentobarbital) laparotomized dog averages 7 7 ± 1.5 mm. Hg.[188] Fishman, Stamler, Katz, Miller, Silber, and Rubenstein [560] find that in trained, unanesthetized, resting dogs this figure ranges from 7 to 9 mm. Hg. This pressure, as measured by renal vein catheterization in 17 normal human subjects, averaged 11.7 mm. Hg (10 to 14.6).[1419] The point of zero reference in these studies was determined roentgenologically to average 9 4 cm. above the table top with the subject in the recumbent position.

* Bush, Coffman, Montgomery, and Swan [205] report that the pressure required to force 1 to 2 cu mm. of saline into the dog kidney through a 20 gauge needle with side perforations averaged 72 mm Hg (range 55 to 88 mm.). Similar values were obtained in cats and rabbits This method in the hands of these investigators yielded intramuscular pressures of 4 to 7 mm. Hg. They do not equate this pressure with the interstitial pressure, however, it is probable that it represents tearing or distortion pressure uniquely related to their technique and having nothing to do with interstitial pressure.

Blake *et al.*[188] found that when the renal venous pressure was increased on one side in the anesthetized (pentobarbital) laparotomized dog, elevation of pressure to 27 mm. Hg had no effect on filtration rate, renal blood flow, Tm_G or Tm_D. (The increased sodium and water reabsorption observed by them under these conditions has been noted in chapter XXII.) In their studies on unanesthetized dogs with pericardial tamponade, Fishman *et al.* find that renal venous pressure may rise to 20 mm. Hg with reduction in filtration rate or renal blood flow. The absence of hemodynamic effects implies that postglomerular dilatation offsets the increased venous pressure. In contrast to these results, however, are those of Selkurt, Hall, and Spencer,[1824] who by similar methods (laparotomized dogs anesthetized with pentobarbital) found that an increase in renal venous pressure from 7.5 to 22.4 mm. Hg decreased the renal blood flow and filtration rate by an average of 15 per cent, a decrease that can be explained almost entirely by the decrease in pressure gradient across the renal vascular circuit, the arterial-venous pressure difference decreasing by an average of 11.5 per cent The PAH and creatinine clearances showed parallel reductions, indicating that elevated renal venous pressure does not increase glomerular pressure.*

In view of these conflicting results, and especially in view of the possibility of initiating changes in renal vasomotor tone by increasing renal venous pressure, it seems impossible to define the pure hemodynamic effects of the latter at the present time except to affirm the conclusion that the increase in renal venous pressure in chronic congestive failure, whatever its effect on sodium reabsorption, cannot explain the observed reduced filtration rate and renal blood flow.†

* Vasomotor changes in the kidney cannot be ruled out, and it is particularly to be noted that in the experiments of Selkurt *et al* the renal plasma flow throughout the period of observation was steadily declining, falling by as much as 30 per cent in 2 hr or so. This fact in itself implies that renal vasomotor changes were somehow initiated by the conditions of the experiment.

† Maxwell, Breed, and Schwartz[1413] report an average renal venous pressure of 22 mm Hg (12 7 to 30 0) in 9 subjects in congestive heart failure, and, as noted in chapter XXII, calculation shows this to be insufficient to reduce the renal blood flow by more than 14 per cent, far less than is observed in most patients in failure

CALCULATION OF RENAL RESISTANCE

Smith, Chasis, Goldring, and Ranges[1934] attempted to treat the problem of renal resistances hemodynamically. They erroneously started with the assumption that filtration equilibrium is necessarily reached in the glomerulus.

In Lamport's[1201,1202] subsequent treatment of this problem he also commits himself to the unwarranted assumption above and introduces a minimal factor of 20 mm Hg plus another 20 mm. intracapsular pressure, both opposing flow Lamport deduces that the conditions required for a constant filtration rate when the renal blood flow is changing are represented by inverse changes in afferent and efferent arterioles This does *not* appear to follow from his own equations and is contrary to hemodynamic principles. The consequences of such inverse changes are illustrated by figure 13 in Gomez'[806] discussion of renal hemodynamics.

Brun, Knudsen, Petersen, and Raaschou[279] have examined the process of filtration in a physical model and translated their observations through hydrodynamic equations to the changes in renal clearances observed in the supine and erect posture. They conclude that the changes in clearance cannot be explained solely by general changes in the pressure and composition of the blood, but must involve changes in efferent arteriolar tone.

The theoretic aspects of renal hemodynamics have subsequently been treated in detail by Gomez[807] as a subordinate phase of general hemodynamics,[806] and the following working equations for the calculation of renal resistances have been derived by him from that analysis.

The application of hemodynamic theory to the calculation of segmental resistances requires certain simplifying assumptions, without which no evaluation whatever can be attempted. These assumptions involve the following considerations:

a. The blood flow is a linear function of pressure only when oth flow and pressure are relatively large, and the calculation of esistances is meaningful only under such conditions. It would eem that one can safely treat flow and pressures down to about e-third and two-thirds of their respective normal values (i.e. o cc. for renal blood flow and 60 mm. Hg for mean arterial essure).

b. The specific coefficient of permeability of a membrane is d[e]fined as the rate of movement of fluid across a unit area per uni[t] pressure per unit time (cc. per sq. cm. per mm. Hg per sec.). Th[e] gross permeability coefficient is the product of the specific permeability coefficient times the total surface area. In comparing two individuals, or the same individual under different circumstances, it must be assumed that the gross permeabilities of both th[e] glomerular bed and peritubular capillaries remain constant, a[nd] an approximate numerical value must be assigned to the form[er]. This assumption of constant gross glomerular permeability is n[ot] applicable to glomerular disease (glomerulonephritis, nephrosis, intercapillary glomerulosclerosis, eclampsia, etc.) and in such instances valid hemodynamic comparisons with the normal kidney cannot be made.

c. The interstitial pressure will in theory remain relatively constant within certain limits of renal blood flow, but it will be dependent on the venous pressure, as specified above. A numerical value must be assigned to the interstitial pressure, an assignment that can be made, so far as the normal kidney is concerned, on the basis of Gottschalk's studies.

d. During filtration, the oncotic pressure of the plasma is increased, and this increase may affect or in turn be modified by a shift of water between the red cells and the plasma. This shift is here neglected and the change in oncotic pressure in the glomeruli is related simply to the fraction of plasma water filtered.

The values of total glomerular permeability, interstitial pressure, and renal venous pressure that must be assumed for purposes of calculation are within wide limits not critical in influencing the qualitative changes in calculated resistances.

e. For practical purposes the renal circulation may be divided into five functional segments:

1. afferent arterioles
2. glomerular capillaries
3. efferent arterioles
4. peritubular capillaries
5. venules

Since these segments are arranged in series, each segment independently contributes its quota of resistance to the total resistance between the renal artery and vein. In general, variations in the resistance offered by any segment may be conceived as resulting chiefly from variations in the total cross-sectional area of that segment, but they will generally be accompanied by passively induced changes in caliber, and therefore in resistance, of other segments.

Hemodynamic theory does not at the present time permit us to calculate the local resistance of the glomerular capillaries or the peritubular capillaries as individual segments, and their contribution to total renal resistance must therefore be subsumed in efferent and venular resistance, respectively. But because of the large number of capillaries involved in both segments, and the relatively slow movement of blood in each capillary, their absolute contribution to resistance is small in comparison with that of the afferent and efferent arterioles and the venules.

Neither can an exact anatomical locus be ascribed to these segments. Rather this locus must be defined functionally, the afferent resistance as the resistance of the arterial and arteriolar bed and some undefined fraction of the glomerular resistance, the latter having a small value relative to the whole, the efferent resistance as the residual glomerular resistance (again very small) plus the resistance of the efferent arteriole and an undefined fraction of the resistance of the peritubular capillaries (again very small); and the venous resistance as the residual peritubular capillary resistance plus the resistance of the venules and veins down to the vena cava (or renal vein) where the renal venous pressure is measured.

The total renal resistance is equal to the sum of the segmental (series) resistances and, in conventional hemodynamic terms, may be calculated as the effective perfusion pressure divided by the blood flow:

$$(1) \qquad R = \frac{P_m - P_v}{Q} \times 1328 = R_A + R'_E + R_V$$

where R = total renal resistance (dynes. sec. cm.$^{-5}$)
R_A = afferent resistance (dynes. sec. cm.$^{-5}$)
R'_E = net efferent resistance (dynes. sec. cm.$^{-5}$) (to be defined below)
R_V = venular resistance (dynes. sec. cm.$^{-5}$)
P_m = mean arterial pressure (mm. Hg)
P_v = renal venous pressure (mm. Hg)
Q = renal blood flow in cc/sec. (all values of Q and of the filtration rate, q, must be corrected to 1.73 sq. m. before incorporation into the equations, because surface area does not factor all the terms in equations 6, 8, and 10.)

The factor 1328 serves to convert blood pressure units (mm. Hg) into absolute units of resistance and is derived by multiplying the acceleration of gravity, G (980.6 cm. sec.$^{-2}$), by the weight of 1 mm. of Hg (13.546 at 20° C.), this product yielding dynes/sq. cm. or barys, which when divided by cc/sec. yields dynes. sec. cm.$^{-5}$

Equation 1 directly yields the total renal resistance, R, by its second member through the clinically determinable values, P_m, P_v, and Q.

VENULAR RESISTANCE, R_V

In order to convert the third member of this equation into one involving clinically determinable data, the first step is to note that the venular resistance, R_V, is the decrement in pressure between the peritubular capillaries and the renal vein, divided by the renal blood flow. Assuming that filtration equilibrium has been very closely approximated in the peritubular capillaries,* the hydrostatic pressure as it enters the venules may be taken as equal to the oncotic pressure plus the interstitial pressure:

$$R_V = \frac{P_t - P_v}{Q} \times 1328 = \frac{H + h - P_v}{Q} \times 1328 \qquad (2)$$

* As must be the case where 85 to 99+ per cent of the water of the glomerular filtrate is reabsorbed by these capillaries

where P_t = the mean hydrostatic pressure at the end of the peritubular capillaries

P_v = the renal venous pressure (or vena caval pressure near the outlet of the renal vein)

h = the mean oncotic pressure in the peritubular capillaries (to be defined below)

H = the interstitial pressure

P_v, if known, is to be taken as measured, or, in the absence of increased peripheral venous pressure, the normal approximate average value of 10 mm Hg may be used; h may be obtained from the protein concentration of systemic blood by applying the following relationships:

(3)

$$C_E = C_A \frac{Q'}{Q' - q}$$

where C_A = the plasma protein concentration (in gm/100 cc.) in afferent blood

Q' = the renal plasma flow

q = the filtration rate (both in cc/1 73 sq. m.)

C_E = the plasma protein concentration in the efferent glomerular blood

The mean protein concentration, C_m, in both the glomerular and peritubular capillaries may be taken as the arithmetical mean between C_A and C_E:

(4)

$$C_m = \frac{C_E + C_A}{2} = C_A \left(\frac{Q' - \frac{q}{2}}{Q' - q} \right)$$

The mean oncotic pressure is calculated from the following empirical formula

(5)

$$h = A[C_m - 2]$$

where A is a factor having the dimension of pressure. This term has been determined from the relationship between oncotic pressure and plasma protein concentration in normal subjects, as recorded by Wells, Youmans, and Miller,[2144] to have an average value of 5 0.

In respect to H, a choice must be made between the alternativ conditions of low and high renal venous pressures: where P_v is les than 10 mm. Hg, H may be taken as constant and equal to 10 mm.; where P_v is equal to or greater than 10 mm., H may be taken as equal to P_v with the important qualification that H may be greater than P_v in renal disease (constrictive perinephritis, etc.) or in the presence of renal edema.

NET EFFERENT RESISTANCE, R'_E

In speaking of the efferent resistance, it will be observed that a quantity, q, of fluid is shunted around the efferent arterioles by glomerular filtration and tubular reabsorption into the peritubular capillaries, this quantity normally amounting to about 10 per cen of the renal blood flow. We must, therefore, distinguish between what would be the true efferent resistance were this shunting ab- sent, and the net efferent resistance as calculated with due allowance for the shunt.

The true efferent resistance, R_E, and the compound total permeability of the glomerular and peritubular capillaries are related in such a manner that R_E is equal to the quotient of the 2 parallel shunts, q and Q − q, divided by $\bar{\lambda}$, the gross permeability of the glomerular capillaries:

(6)

$$R_E = \frac{q}{\bar{\lambda}(Q - q)} \times 1328$$

The approximate value of $\bar{\lambda}$ is 0.0812, this value (which is the inverse of a resistance) being derived from the average filtration rate of 130 cc/min. and the assumed intraglomerular pressure of 60 mm. Hg.* Any error in this assumed value will affect all calculated resistances equally so long as H is fixed and therefore will not distort the calculation of relative resistances.

The net efferent resistance, R'_E, is that presented by the parallel combination of the efferent arteriolar segment and the shunt through the glomerulus and peritubular capillaries. R'_E, R_E, and λ are connected through the conventional relation for parallel re-

* $\bar{\lambda} = \frac{q}{P_g - h - H}$ where P_g is the glomerular pressure, here taken as 60 mm. Hg, q is here taken as 2 167 cc/sec , h as 25, and H as 10 mm. Hg.

sistances by the equation

(7)

$$R'_E = \frac{R_E \times 1328}{\lambda R_E + 1328} = \frac{R_E}{\frac{\lambda R_E}{1328} + 1}$$

Substituting (6) in (7)

(8)

$$R'_E = R_E \frac{Q - q}{Q}$$

AFFERENT RESISTANCE, R_A

From equation (1)

(9)

$$R_A = R - (R_V + R'_E)$$

Alternatively, replacing R, R_A, and R'_E by their respective values as obtained from the second member of (1), from the third member of (2), and from (8),

(10)

$$R_A = \frac{1328}{Q}\left[P_m - \left(H + h + \frac{q}{\lambda}\right)\right]$$

all the terms of which are clinically determinable.*

GLOMERULAR DYNAMICS IN THE NORMAL HUMAN KIDNEY

NORMAL VALUES OF RENAL RESISTANCES

Normal values of renal resistances, calculated from the averaged data on renal clearances recorded on normal subjects by Goldring

* In this derivation, plasma flow is to be taken as equal to the diodrast or PAH clearance uncorrected for E_D or E_{PAH}. In the normal kidney, the fact that E is less than 1.0 may be in great part attributed to shunting of blood around the excretory tissue of the kidney (i.e. through the perirenal fat, capsule, etc.) and this extrarenal circulation may be treated as a shunt, the resistance of which, R_s, is

(11)

$$R_s = E\frac{P_m - P_V}{(1 - E)Q} \times 1328$$

The net parallel resistance, R_W, of the kidney including this shunt is then

(12)

$$R_W = \frac{RR_s}{R + R_s} = E\frac{(P_m - P_V)}{Q} \times 1328$$

et al.[197] by assuming P_m = 90 mm. Hg, are given as series I in tab
XVII. Series II of this table represents similar calculations from th

TABLE XVII

Renal Resistances

	Normal subjects: Series I, Data from Goldring *et al.*[197] $\times 10^4$	Normal subjects: Series II, Data from Bolomey *et al.*[207] $\times 10^4$	Hypertensive subjects: Series III, Data from Bolomey *et al.*[207] $\times 10^4$	Hypertensive subjects: Per cent increase relative to series II
R	5.31	6.97	17.2	147
R_A	1.99	3.17	11.3	256
R'_E	1.66	1.91	2.98	56
R_V	1.66	1.88	2.98	58

averaged data recorded by Bolomey *et al.*,[207] using the observed average blood pressure of 92 mm. Hg.

Figure 111 shows the mean pressures to be expected at the end of various renal segments when all critical terms are given arbitrary values.

ESSENTIAL HYPERTENSION

Average clearance data on 26 subjects with essential hypertension (P_m = 145 mm. Hg) are given by Bolomey *et al.*[207] The renal resistances calculated from the mean values for the entire series are given in table XVII. It will be seen that, relative to series II, in these hypertensive subjects R is increased by 147 per cent, R_A by 256 per cent, R'_E by 56 per cent, and R_V by 58 per cent.

Were the 'normal' kidney, represented by series II, perfused at a mean pressure of 145 mm. Hg, as in the hypertensive subjects, and the resistances not changed, the filtration rate would be increased from 123 to 178 cc., the renal blood flow from 1052 to 1545 cc., and the filtration fraction from 0.190 to 0.280.

Conversely, were the perfusion pressure of the hypertensive kidney (series III) reduced to the normal value of 92 mm. Hg (as in series II), the filtration rate would decrease from 79.8 to below 38 cc. and the renal blood flow from 670 to below 378 cc., these terminal figures probably being too high because of the passive diminution in the diameter of the vessels at the reduced pressure.

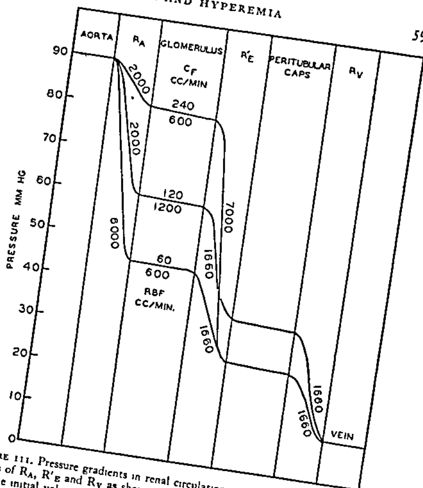


FIGURE 111. Pressure gradients in renal circulation, calculated for the selected values of R_A, R'_E and R_V as shown, and H = 10 mm Hg, C_A = 6 5 gm/100 cc The initial value of h for the mid-curve is 24 mm. Hg, this term varying with the imposed new resistances

RENAL ISCHEMIA AND HYPEREMIA

Numerous data are available on the diodrast and inulin clearances in normal subjects under various conditions of renal blood flow. These data may be divided into three groups: (1) observations made during standard conditions by Goldring *et al.*,[111] which w... hall designate as 'basal,' with the reservations concerning the us...

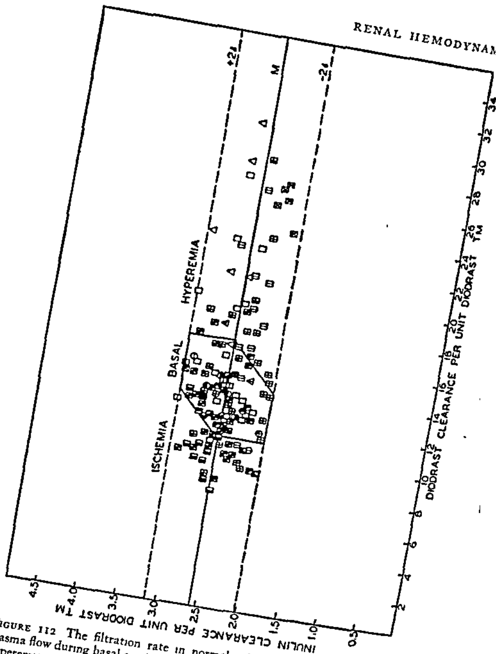


FIGURE 112 The filtration rate in normal subjects in relation to the renal plasma flow during basal conditions, ischemia induced by adrenalin and pyrexial hyperemia.

On the assumption that diodrast Tm, which is a measure of the total tubular excretory tissue in the kidney, is closely proportional to the total renal weight,

of this word stated by the authors; (2) observations made during the reduced renal blood flow induced by adrenalin, neosynephrin, and marked apprehension, and here referred to as 'ischemia'; and (3) observations made during the increased renal blood flow induced by the pyrexial reaction and here designated as 'hyperemia.'

These data are presented in figure 112. Each datum contained in the 'basal' group is the average of 3 or more consecutive clearance periods, each subject being recorded as often as examined. Each datum referable to 'ischemia' or 'hyperemia' is the average of at least 2 successive clearance periods obtained during reduced or increased renal blood flow, each subject thus contributing several data from each occasion on which ischemia or hyperemia was induced. Goldring *et al.* reported, in 35 men and women, the average value of $C_{IN}/Tm_D = 2.56 \pm 0.28$ cc/min.; for purposes of comparison this mean is indicated by a solid line with twice the standard deviation (dashed lines). This mean ratio includes only observations made under 'basal' conditions, and in its calculation each subject enters only once, thus contributing to the mean only his or her average behavior.

It is evident from figure 112 that the ratio C_{IN}/Tm_D at all renal blood flows is adequately contained within the statistical parameters of the 'basal' data. It may therefore be said that the filtration rate remains essentially constant during ischemia and hyperemia induced by the measures specifically stated. (It is not implied that this constancy will obtain if ischemia or hyperemia is induced by measures other than those stated, and indeed such is not the case.)

In consequence of the constancy of the filtration rate, the filtration fraction shows a reciprocal relation to renal blood flow,



Each datum represents the average of 2 or more clearance periods, each subject furnishing several data on each examination under ischemia or hyperemia

The hexagon is an arbitrary area which encloses 95 per cent of the basal observations (Smith, Chasis, Goldring, and Ranges [114])

the two variables, C_{IN}/C_D and C_D/Tm_D, necessarily generating a rectangular hyperbole as shown in figure 113.

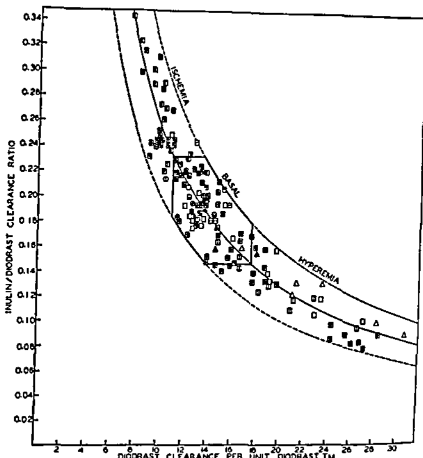


FIGURE 113. The filtration fraction in relation to renal plasma flow per unit Tm_D. The solid curve represents the course of the filtration fraction if the filtration rate remains constant (see fig 114); i.e if $C_{IN}/C_D \times C_D/Tm_D = C_{IN}/Tm_D =$ 2 56. The dotted lines represent this mean value $\pm 2\sigma$ The hexagon is an arbitrary area which contains 95 per cent of the normal data obtained under basal conditions, under adrenalin, the filtration fraction rises above the limits of the hexagon, during hyperemia it falls below, but in both instances it remains within the normal parameters (Smith, Chasis, Goldring, and Ranges [1934])

The hemodynamic sequence in the kidney which gives rise to a relationship such as is shown in figures 112 and 113 can best be grasped from figure 114, which represents the changes in filtration

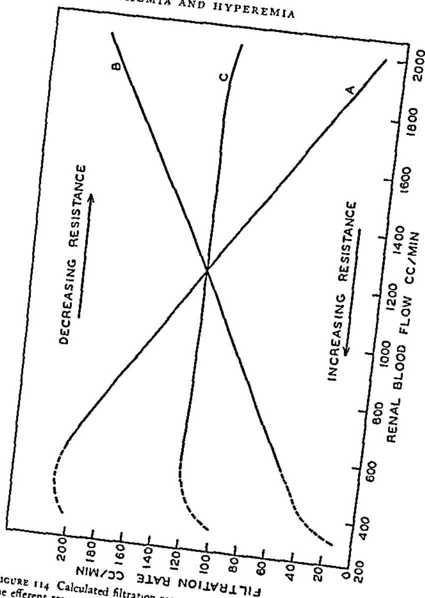


FIGURE 114 Calculated filtration rate in relation to renal blood flow (A) when the efferent resistance alone is changed, (B) when the afferent resistance alone is changed, and (C) when both resistances are changed proportionally. At the normal point of departure the renal characteristics are as follows. $R_A = 1.99 \times$

to be expected from changing only (a) efferent arteriolar resistance, (b) afferent arteriolar resistance, and (c) by equal changes in both segments. In constructing this figure, arbitrary values were taken for the median point, the renal blood flow, filtration rate, R_A, and R'_E, while R_V was taken as constant throughout. When the renal blood is reduced by pure efferent constriction, the filtration rate increases. This is because any increase in R'_E is accompanied by an increase in glomerular pressure and consequently in the filtration fraction. Conversely, when the renal blood flow is reduced by pure afferent constriction the filtration rate decreases. Exactly equal changes in R'_E and R_A result in only a moderate increase in filtration rate as the renal blood flow is decreased from large to small values lying within the physiological range of hyperemia and ischemia, shown in figure 112.

The changes in filtration fraction corresponding to the foregoing changes in resistance are shown in figure 115.

It must be concluded that, contrary to the conclusion of Smith *et al.*,[1934] the functional changes in renal blood flow associated with hyperemia and adrenergic ischemia represent approximately equal changes in R_A and R'_E, *disregarding changes in* R_V.

Data derived from unpublished studies by Gomez, Maxwell, Fishman, Morales, and Crowder, obtained during the intravenous infusion of adrenalin are given in figure 116. The data shown at A give the segmental resistances in absolute units during the control period. Moderate reduction in renal blood flow was effected by adrenalin at B without reduction of filtration rate. This is perhaps the most frequently observed effect of moderate doses of adrenalin, as shown in figure 77. At this time R_A had increased by 19.2 per cent, R'_E by 37.7 per cent, and R_V by 34.5 per cent. At C, where the renal ischemia was most marked and the filtration rate was somewhat reduced, these increments were 81.6, 49.6, and 109 3 per cent respectively.

Thus the most marked effect of adrenalin at the peak of its

10^3, R_E = 1 66 x 10^3 and R_V = 1 66 x 10^3, C_F = 120 and RBF = 1200 cc/min, H = 10 mm. Hg The initial value of the mean oncotic pressure, h, is 24 mm. Hg, but this value is dependent on the changes in resistance which are imposed on the system, being determined by the derived values of filtration rate and renal plasma flow.

action was upon the venular resistance, the effect on the efferent segment being intermediate in intensity. (It cannot be supposed that this is the invariable action of adrenalin; larger doses might have a qualitatively different effect.) This increase in venular re-

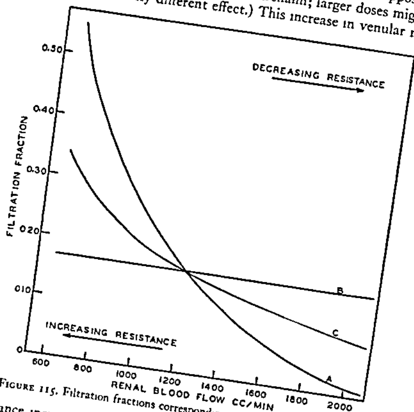


FIGURE 115. Filtration fractions corresponding to the data in figure 114.

sistance increases the pressure in the peritubular capillaries and opposes the reabsorption of water, leading to an increase in the volume of the interstitial fluid. It is this expansion of the interstitial fluid, rather than an increase in volume of the glomeruli, which we conceive to be the explanation of the paradoxical increase in volume of the kidney under the action of adrenalin as first described by Richards and Plant [173]

Figure 117 shows a normal subject examined during pyrexial hyperemia induced by the intravenous administration of 75 mil-

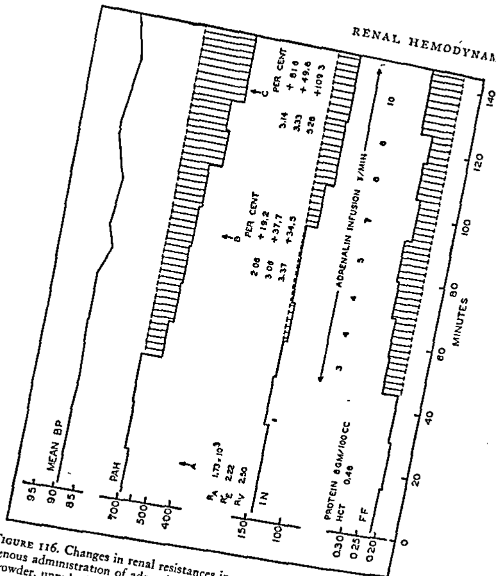


Figure 116. Changes in renal resistances in a normal subject during the intravenous administration of adrenalin. (Gomez, Maxwell, Fishman, Morales, and Crowder, unpub. data)

lion triple typhoid vaccine. The patient had been premedicated with amidopyrine, 10 grains every 4 hr. from noon the day before until 8 A.M. on the day of the test (see also figures 83 and 84). As usual, renal hyperemia follows only after a long latent period. At B, about the time at which the chill would have occurred in an un-

premedicated subject, the blood pressure decreased significantly, this period of hypotension being accompanied by a transient reduction in the filtration rate. At B, R_A had decreased by 34.7 per cent, while R'_E and R_V had increased by 102 and 169 per cent, respectively. At C all 3 resistances had decreased by 52.7, 44, and 55 per cent respectively.

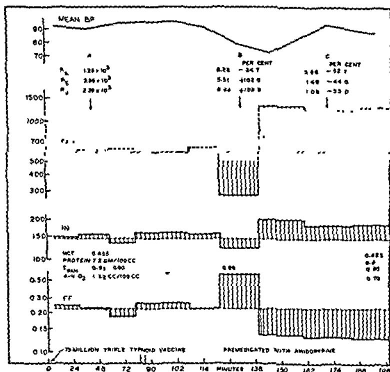


FIGURE 117 Changes in renal resistances in a normal subject during pyrexial hyperemia (Gomez, Maxwell, Fishman, Morales, and Crowder, unpub data)

CONGESTIVE HEART FAILURE

Figure 118 shows observations in a subject in the edematous state of chronic congestive heart failure. As noted in chapter XII, in this condition the renal blood flow and filtration rate are markedly reduced. In this particular patient, all resistances were increased

over normal, R_V somewhat more than R_A and R'_E. Paracentesis of 3700 cc. of ascitic fluid had no effect on renal function, and neither did phlebotomy, despite the fact that the latter caused a decrease in peripheral venous pressure from 30 to 20 mm. Hg.

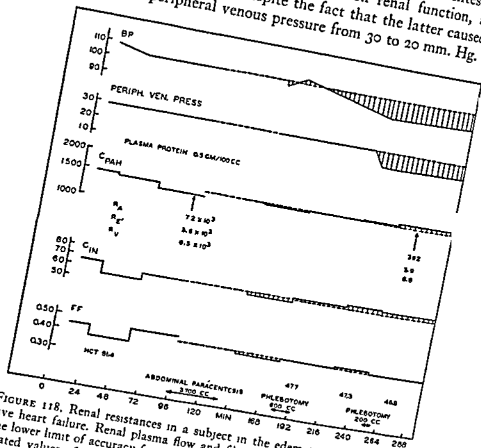


FIGURE 118. Renal resistances in a subject in the edematous state of congestive heart failure. Renal plasma flow and filtration rate in this patient are at the lower limit of accuracy for the use of hemodynamic equations and the estimated values of R may be inaccurate. (Gomez, Maxwell, Fishman, Morales, and Crowder, unpub data)

These studies show that all three vascular segments are involved in spontaneous changes in renal blood flow and in those which accompany adrenalin ischemia of moderate intensity and pyrexial hyperemia.* The present data lead us to infer, and at the moment it can be no more than an inference, that the muscularly active

* It may be recalled that adrenalin ischemia and pyrexial hyperemia are essentially unmodified in the denervated human kidney (ch. XIV).

segments of the renal circulation, the afferent and efferent arterioles and veins, comprise an integrated system which generally operates, in the interests of glomerular-tubular balance, to maintain a constant filtration rate. In view of the evidence of the autonomy of the renal circulation (ch. XIV) this integration appears to be worked out between these vascular segments essentially without extrarenal aid. It will bear repeating that, by the present evidence, the chief consideration in glomerular-tubular balance appears to be the maintenance of salt and water balance. But, apart from implications involving the extracellular fluid (ch. XI), how these changes in the renal vasculature are initiated remains a mystery, and it is therefore impossible at the present time to interpret the changes in pathological states such as essential hypertension and congestive heart failure.

Part IV

CHAPTER XIX

Limitations of Clearance Methods during Disturbed Renal Function

In interpreting the results obtained in the diseased kidney by clearance methods, the limitations of these methods must be clearly kept in mind. These limitations were emphasized by the writer [1910] in an early paper which has apparently not been too widely read.

It will aid in this discussion if certain concepts are given sharp definition, even though these concepts may prove to be oversimplified (fig. 119).

One may speak of a *normal, active nephron* as one in which the glomerulus and tubule are functioning in the formation of glomerular filtrate and in the tubular excretion or reabsorption of some particular solute. The glomeruli and tubules of normal nephrons may become partly or wholly inactive as a result of local ischemia without losing their potentiality for immediate return of function on the restoration of an adequate blood supply.

An *aglomerular tubule* is one in which excretory function and urine formation persist after destruction of the adjoined glomerulus. There is as yet no functional evidence of the existence of aglomerular tubules in the normal or diseased human kidney. It remains to be demonstrated whether or not the mammalian nephron, which normally reabsorbs water, can under any circumstances excrete it, and the tubular excretion of water must be pre-

supposed if the term 'aglomerular nephron' is to have any significance. If water is excreted by the tubules in the mammals, tubules temporarily rendered *inactive* by functional cessation of the attached glomeruli might fall in this category. In the absence of tubular water excretion, such *inactive* nephrons would fall in the category of *inert* tissue.

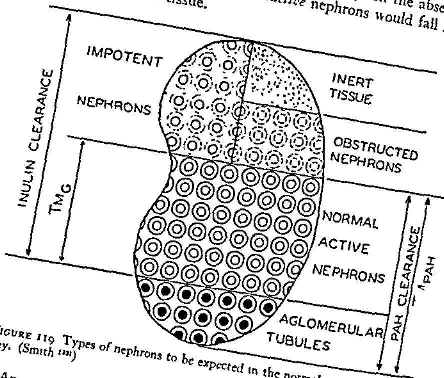


FIGURE 119 Types of nephrons to be expected in the normal and diseased kidney. (Smith 111)

An *impotent nephron* is conceived as one in which the tubule remains anatomically intact and connected with an active glomerulus and a patent collecting duct, but in which the capacity to reabsorb or excrete one or more substances has been lost. It is possible that the tubular transport of some test substance (diodrast, PAH, etc.) might be lost without the transport of other substances being affected, but in general unfavorable circumstances, such as ischemia, toxic substances, atrophy, etc., may be expected to affect all mechanisms of tubular transport in any one tubule cell in a qualitatively similar manner. Where all tubular reabsorptive activity is lost, the tubule would act as a passive conduit to drain

glomerular filtrate into the urine. The occurrence of large numbers of impotent nephrons is indicated in the early recovery phase following anuria, where a dilute urine, not differing greatly from glomerular filtrate, is excreted. Permeable nephrons, in which glomerular filtrate continues to be formed but all or nearly all of the constituents, including water, escape through injured tubules, would fall into the above category, but would not contribute to the formation of urine.

Obstructed nephrons represent those in which protein casts have obstructed the tubule or collecting ducts. Presumably the earlier portions of such tubules would suffer some increase in permeability or loss of transport power.

Non-excretory renal tissue perfused by blood flowing from the renal artery to the renal vein may be designated as *inert tissue*. This would include the renal capsule, perirenal fat, non-excretory circulatory channels through the renal pelvis and calyces, impotent nephrons, permeable nephrons and obstructed nephrons, as defined above, and fibrotic glomeruli and tubular fragments generally.

Since there are two million-odd nephrons in the two kidneys, it is self-evident that no overall method of examination can directly reveal what is occurring in individual nephrons. Impairment in any clearance function may be the result of the partial reduction of function in all nephrons or the complete reduction of function in a few. Conversely, constancy of function does not imply constancy in all contributing nephrons, since function may be increased in some nephrons at a time when it is decreased in others.

Since a variable quantity of water is reabsorbed by the tubule, it is impossible, either in a single nephron or in the total kidneys, to deduce from the urine flow how much water has been filtered from the blood. The rate of filtration can be deduced in either case only by means of an appropriate standard of reference, namely a completely filtrable solute which is neither reabsorbed nor excreted by the tubule; and, in turn, the selection of this standard of reference can be made only by a comparison of clearances of various substances with different diffusion coefficients and potentialities for tubular reabsorption or excretion.

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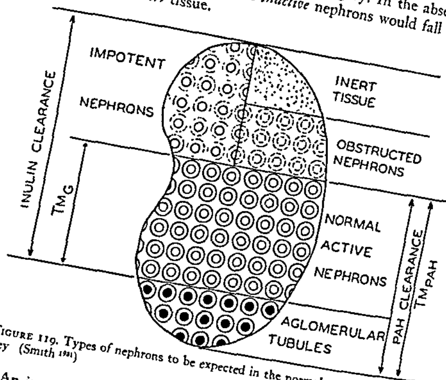


FIGURE 119. Types of nephrons to be expected in the normal and diseased kidney (Smith 1951)

An *impotent nephron* is conceived as one in which the tubule remains anatomically intact and connected with an active glomerulus and a patent collecting duct, but in which the capacity to reabsorb or excrete one or more substances has been lost. It is possible that the tubular transport of some test substance (diodrast, PAH, etc.) might be lost without the transport of other substances being affected, but in general unfavorable circumstances, such as ischemia, toxic substances, atrophy, etc., may be expected to affect all mechanisms of tubular transport in any one tubule cell in a qualitatively similar manner. Where all tubular reabsorptive activity is lost, the tubule would act as a passive conduit to drain

normal nephrons. With regard to diffusion, a concentration gradient will be established between the capillary adjacent to the impotent tubule and some other normal tubule; as long as the plasma concentration of PAH is constant, the actual time required for a PAH molecule to move the length of this gradient may be neglected and the radius of effective diffusion may be conceived to be limited only by a physical interruption of the diffusion freeway. The PAH cleared by a particular tubule may have diffused out of a remote capillary, *and the concentration of PAH in that capillary* will continue to decrease as the blood moves distally.

With regard to the circulation of interstitial fluid, it will be noted that, out of 127 cc. of filtrate formed each minute, the greater fraction is reabsorbed by the tubules and must pass across the interstitial space to the capillary bed before it re-enters the blood. It is scarcely probable that this circulation of interstitial fluid occurs along the shortest possible point-to-point route; on the contrary, there must be a considerable streaming between or along the tubules, which is aided by the arterial pulse. This streaming will not only accelerate the movement of PAH from capillary to excretory tubule, but it may also increase the radius of clearance considerably beyond that which diffusion alone would permit. Although diffusion and circulation of renal interstitial fluid must play an important role in normal renal function, they are possibly of greater significance in the diseased kidney.

It is conceivable that loss of excretory activity may occur in large areas affecting many tubules, in short stretches of single tubules, or even in single tubule cells, and, except for the first circumstance, interstitial circulation may be important in maintaining a high extraction ratio. This appears to be the case, for example, in essential hypertension, where E_{PAH} remains normal despite considerable destruction of excretory tissue as measured by Tm_{PAH}

Any circumstance that restricts the circulation of interstitial fluid (increased intrarenal pressure, edema, perinephritis, etc.) would be equivalent to a reduction in actual blood flow to such areas in the kidney as might be dependent on this circulation rather than on a direct blood supply for their perfusion. But in

In the diseased kidney, an increase in permeability of the tubule may permit the escape of water from the tubular urine without permitting the escape of inulin; and, conversely, a decrease in permeability of the glomerular membranes may retard the filtration of inulin without proportionally retarding the filtration of water; in either case, the differential movement of water cannot be detected by changes in C_{IN}, although, if decreased glomerular permeability can be ruled out, it may conceivably be deduced by the comparison of the inulin clearance with the clearance of some smaller molecule. The parallel behavior of urea and inulin in all stages of chronic diffuse glomerulonephritis indicates that the reduced excretion of both substances is primarily attributable to the obliteration of glomeruli rather than increased back diffusion of urea.[363] In acute nephritis, however, the urea/inulin clearance ratio may be abnormally low, indicating increased permeability to urea and possibly some increased permeability to inulin.

Lastly, it is conceivable that filtration may continue in a glomerulus after the attached tubule has become separated from its collecting duct, or that the tubule may become so permeable that all the constituents in the glomerular filtrate, including inulin, escape into the interstitial fluid rather than the urine. The inulin clearance represents only such inulin as is passed into the bladder and will reveal nothing of these circumstances. Whatever significance the complete local reabsorption of glomerular filtrate may have in renal pathology, it remains beyond the possibility of examination as long as only the total urine is available for analysis.

The PAH (or diodrast) clearance has been defined as the virtual volume of plasma completely cleared of PAH per unit of time. This virtual volume is less than the actual renal plasma flow through the kidney as a whole, because some blood passes from renal artery to renal vein (normally about 9 per cent) by way of inert tissue. Inasmuch as the PAH clearance approaches in magnitude the total renal plasma flow, it affords a method of measuring the latter, subject only to the qualification that the extraction ratio (normally 91 per cent) remains constant.

If a nephron loses its excretory power, the blood which once was cleared by that nephron may, through diffusion of PAH or circulation of interstitial fluid, continue to be cleared by neighboring

this is measured at high plasma concentrations. These same considerations apply to blood exclusively perfusing inert tissue; * if particular PAH molecules are not brought into effective juxtaposition with functional excretory tissue for clearance at a low plasma concentration, in general † they will not be made available for clearance simply in consequence of increasing the plasma concentration; i.e. any tissue incapable of excreting PAH at low plasma concentration will not acquire excretory capacity because of an increased PAH concentration In general, therefore, where the plasma concentration is the only changing factor, inert tissue is excluded from both the PAH clearance and Tm_{PAH}; hence, in the measurement of these two values, the same vascular and interstitial channels are involved, and the two values refer to the same nephrons or lesser units of excretory activity. Whether Tm_{PAH} is conceived in terms of entire nephrons, individual cells, or hypothetical excretory units of minimal dimensions is immaterial; the

* The terms 'exclusively perfusing' exclude diffusion through and circulation of the interstitial fluid, while the terms 'inert tissue' exclude normal tubular tissue which is inactive simply because of ischemia or because it is presented only with blood that has previously been cleared

† It is possible that a decrease in permeability of the capillaries, interstitial tissue, or tubule cell, or some change in the tubular excretory mechanism itself, could retard the movement of PAH from blood to tubular urine, since the blood is available for clearance in the peritubular capillary for only a brief period, this retardation would lower the fraction of the PAH removed during its passage down this capillary But, whether the retarding factor is a positive barrier (i e relatively impermeable connective tissue) or a negative fault (e g. failure of the tubule cell to handle all molecules presented to it), it is reasonable to expect that the retardation would operate on any and all molecules with statistical indifference, with the result that the clearance probabilities for any particular molecule would not be increased by increasing the number of molecules

Exceptions to this statement are conceivable, one might imagine that at a low concentration so large a fraction of PAH was absorbed on the plasma protein that escape from the capillary by diffusion was greatly retarded and the extraction ratio correspondingly reduced, if, at some higher concentration the plasma proteins became saturated, the diffusion of PAH from the capillary, and consequently the extraction ratio, would be increased Since protein binding is a function of plasma concentration, this particular situation, chosen for illustration only, is not to be expected in practice. Whether or not, as a result of disease, a change in the kinetics of the tubular excretory process could have this consequence is undetermined, but it would seem that the problem can be examined by the progressive elevation of the plasma PAH level. Such titrations as have been recorded to date have supplied no evidence of this situation

general it need not be expected that the extraction ratio will necessarily decrease *pari passu* with focal injury of tubular tissue.

The increased volume of plasma that is made available for clearance by normal tubules in consequence of the formation of impotent nephrons will appear in clearance tests as an apparent hyperemia of the residual functional tissue (increase in C_{PAH} relative to Tm_{PAH}); but, unlike the hyperemia resulting from dilatation of the renal arterioles or increased perfusion pressure, this apparent hyperemia may not afford the normal tubules a proportionately increased supply of oxygen, etc., and it seems advisable to distinguish it from true hyperemia (vascular dilatation) by qualifying it as a vicarious clearance. Failing vicarious clearance, the destruction of renal parenchyma without parallel destruction of the vascular bed will tend to reduce the extraction ratio of PAH, and this ratio may, in the diseased kidney, have any value between the normal value and zero. In considering the diseased kidney as a whole, the PAH clearance will have no certain relation to the total plasma flow unless it is corrected by the extraction ratio

This circumstance does not, however, impair the usefulness of the clearance method; on the contrary, under these conditions the clearance method acquires unique physiological significance. It will aid the reader to visualize the argument if, as an extreme example, it is imagined that an inert tube is inserted between the renal artery and the renal vein of a normal kidney, so that some large fraction of the renal arterial blood passes directly to the renal vein by way of this tube. Since the clearance method depends upon the presence of living excretory tissue to remove PAH from the blood and excrete it in the urine, in the absence of knowledge of the extraction ratio, this method will not reveal how much blood passes from renal artery to renal vein through the inert tube. Nor will the tube begin to excrete PAH when the plasma concentration is raised; i.e. it will not only fail to contribute to the PAH clearance such PAH as is carried by the blood passing through it at low concentrations, but it will also fail to contribute to Tm_{PAH} when

* This circumstance was recognized in our original description of the diodrast learance method 1938 and was the basis of the definition of this clearance as e *effective* renal blood, i e. the *virtual* volume of blood that is completely cleared diodrast.

CHAPTER XX

Primary Disturbances of Salt and Water Balance

OSMOTIC DIURESIS

All vertebrates can excrete a urine that varies from marked hypotonicity to isotonicity with the blood, whereas only mammals,[1923] and to a lesser extent birds,[1141] can elaborate a hypertonic urine. Thermodynamic work is performed in the elaboration of a dilute urine by abstracting urinary solutes from water, and in the elaboration of a hypertonic urine by abstracting water from urinary solutes In both cases the energy is presumably derived entirely from the metabolism of the tubule cells

Among the mammals, the active (distal) reabsorption of water can produce a urine with considerable osmotic pressure. When the distal load of water is small, the extent to which the distal urine can be concentrated is apparently limited by the total osmotic pressure of the tubular urine, the osmotically active constituents that are not reabsorbed will prevent the complete reabsorption of water and thus place a lower limit upon the rate of urine formation Normally the chief osmotically active constituent of the urine is urea, and it is perhaps to the advantage of the organism that at very low urine flows a considerable fraction of the filtered urine is reabsorbed, since in extreme dehydration this circumstance permits water excretion to decrease to lower levels than it otherwise could.

ratio C_{PAH}/Tm_{PAH} expresses the virtual quantity of plasma completely cleared of PAH per unit quantity of the excretory tissue which is effecting the clearance. Hence C_{PAH} and Tm_{PAH} have the same significance in the diseased as in the normal kidney, in which, as emphasized above, there is already some inert tissue and some uncleared blood; if in disease a larger proportion of blood perfuses inert tissue and escapes uncleared, the significance of this ratio remains unchanged.

Thus, a reduction in the overall extraction ratio of PAH in the diseased kidney does not seriously impair the usefulness of the clearance method. On the contrary, this method is the only one capable of determining the volume of blood cleared by such functional excretory units as are inextricably mixed with scar tissue, tubular detritus, connective tissue, etc., a datum upon which no information could be gained by the measurement of the total renal blood flow. When the PAH clearance is referred to the total quantity of available functional tissue by utilization of the ratio C_{PAH}/Tm_{PAH}, a datum is obtained that in most instances will be qualitatively and quantitatively comparable with observations made on the normal kidneys. Even in normal subjects, C_{PAH} should be related to Tm_{PAH} in order to take into account the varying quantities of excretory tissue that may be expected to occur in different individuals.

Although the PAH clearance *per se* cannot afford a reliable index of the total renal plasma flow in the diseased kidney, because of the possible reduction in the extraction ratio, if the extraction ratio is known, the total renal plasma flow can be calculated by dividing the clearance by the extraction ratio (i.e. C_{PAH}/E_{PAH}). This remains reliable in principle so long as both terms can be accurately measured, but in practice a large error is involved when the extraction ratio is small because this term must be determined by difference. When the extraction ratio is zero, the calculation of course becomes mathematically absurd.

tinguished, and we shall first consider the circumstances associated with (b).

Evidence has been presented in chapter XI that, as the load of water delivered from the proximal system to the distal tubule is increased, distal reabsorption remaining fixed in rate, a progressively smaller fraction of this water is reabsorbed and the osmotic pressure of the bladder urine approaches that of the proximal urine (or plasma).[2171] The load of water delivered to the distal tubule will be conditioned not only by proximal water reabsorption but, proximal reabsorption remaining constant so far as sodium and water are concerned, by the filtration rate. Thus, during maximal ADH activity the urine flow may be expected to be in some measure sensitive to the filtration rate. Shannon's[1861,1862] data show that (a) in a normal dog during the post-diuretic phase, the urine flow returns to oliguric levels only when the filtration rate (and distal load of water) decreases, and independently of the urine chloride concentration and osmotic pressure; (b) when a diabetes insipidus dog that is receiving large amounts of ADH (20 to 200 milliunits/hr.) is given water, the urine flow increases with the filtration rate but without concomitant increase in urinary sodium, chloride, or osmotic pressure; (c) when a diabetes insipidus dog is given saline, the urine flow increases with increasing filtration rate, again independently of the concentration of sodium in the urine. The facts all conform with the foregoing interpretation.

The fact that during osmotic diuresis the urine is relatively dilute has been recorded by several investigators. Shannon[1854] observed that, during glucose diuresis in the dog, the glucose concentration in the urine was less than 5 per cent ($\Delta = -0.517°$ C.), although the dog kidney during physiological oliguria can elaborate a urine with $\Delta = -3.0°$ C. Δ in the urine of the rabbit maintained on a diet of oats, bran, and cabbage averaged $-2.543 \pm 0.536°$ C., with an extreme value of $-3.556°$ C.,[851] and yet during sucrose diuresis combined with ADH the maximal value is about 0.8° C.[1801] During dehydration Δ in the urine of the rat may reach $-4.5°$ C., but during sodium chloride or urea diuresis this figure decreases to $-2.7°$ C. or less. This phenomenon does not occur in the newborn

The expression 'osmotic diuresis' has been used to designate the increased urine flow evoked by the intravenous administration of hypertonic sodium chloride, sodium sulphate, urea, sucrose, mannitol, etc., during marked glucosuria and under other similar conditions where the urine is loaded with an osmotically active constituent. However, the expression should not be interpreted as indicating that the urine under these conditions is maximally concentrated; on the contrary, with the progressive development of diuresis the osmotic pressure of the urine decreases, approaching that of the plasma as a limiting value. During all osmotic diuresis the urine is more dilute than during oliguria, when the excretion of all substances is minimal. The mechanism of osmotic diuresis must be sought primarily in the proximal system, where the osmotic agent reduces water reabsorption by its osmotic action,* and, by dilution of the proximal urine, retards the reabsorption of sodium which now adds its osmotic force to that of the primary agent in opposing the reabsorption of water.† Consequently, the quantity of water delivered to the distal tubule exceeds its reabsorptive capacity and the excess is excreted in the urine.

Under normal conditions of hydropenia, the osmotic pressure of the urine is determined by the relative quantities of water and solute (chiefly sodium chloride) reabsorbed by the distal tubule. Activation of the distal tubule by ADH leads to maximal water reabsorption and consequently to maximal concentration of the urine. Water continues to be excreted in small amounts either (a) because of the local restraint offered by the osmotic pressure of urea and other urinary constituents (limiting osmotic pressure of the urine in the strict sense), or (b) because the load of water delivered from the thin limb into the distal tubule exceeds by some small amount the reabsorptive capacity of the latter (osmotic diuresis). Despite difficulties, (a) and (b) can probably be dis-

* Shannon [1854] was apparently the first to state explicitly that any unreabsorbed, osmotically active agent in the glomerular filtrate would retard the reabsorption of water in the proximal tubule.

† Stehle and Melville [1896] have used glucose and mercury bichloride diuresis in an attempt to obtain urine flows in the dog equal to the rate of filtration. They made no attempt, however, to measure the filtration rate and their estimated filtration fraction of 13 per cent is only about half of the known value.

The same relations are displayed more extensively in the data of Rapoport, Brodsky, West, and Mackler,[1078,1080] who studied the osmotic pressure of the urine in boys under conditions of hydropenia and after the administration of urea, glucose, creatinine, sorbose, mannitol, xylose, sucrose, sorbitol, sodium chloride, sodium sulphate, or sodium p-aminohippurate. From oliguria to extreme osmotic diuresis, the rate of urine flow bears a fairly uniform curvilinear relation to the urinary load of solutes, expressed as mosm/min. The authors apply to this relationship an empirical exponential equation based upon the facts, first, that the urine concentration decreases as the load (UV) increases, and, second, that the urine concentration decreases toward that of the plasma as an asymptote. There are, however, an infinite number of pathways by which the asymptote may be approached, and the selection of the simplest exponential function, as made by these authors, is arbitrary and justifiable only on the grounds of convenience. The facts that the equation so constructed permits the prediction of loads representing maximal thermodynamic 'work,' and that low 'work' coincides with low flows, give their equation no physiological significance since these deductions would issue from any other equation of an asymptotic character.

The fact that the urine concentration decreases as the load (UV) increases may be related, in the present view, to the fact that as proximal diuresis increases and floods the distal system, the operations of the latter in reabsorbing water, being limited in rate, become of diminishing importance in changing the composition of the proximal urine, and with large flows the osmotic pressure of the bladder urine must approach that of the proximal urine, which under these conditions is itself isosmotic with the plasma. Any calculation of the precise osmotic pressure to be expected in the urine at various stages of osmotic diuresis must take into account the load of solute and water delivered to the distal system and the limitations in the reabsorption of solute and water by the latter. Such a calculation cannot profitably be made until the operations of the distal system are better understood.

Many older observations may be reinterpreted in the light of the facts above. Thus the observations of Davies, Haldane, and Peskett[93] that the maximal urinary concentration of chloride or

animal (rats and human infants) because during oliguria the urine has an osmotic pressure scarcely more than that of the plasma.[482, 959, 987, 1294, 1296, 1308]

Adolph[27] found that during starvation and thirst the maximal concentration of the urine in man was about 1.2 osm. but the maximal concentration of chloride during thirst, when sodium chloride was ingested, was 0.662 osm., and 0.782 when urea was ingested. Similarly, Black, McCance, and Young[182, 1303] and McCance[1294] found that when the intake of sodium chloride was reduced below the normal level in men enduring water deprivation for 3 to 4 days (or when urea was administered), the average osmotic pressure of the urine remained so nearly constant that they regarded it as maximal and considered the oliguria to be limited by this osmotic pressure. However, when sodium chloride was administered, the chloride content of the urine rose to its recognized maximum of about 0.34 M/liter and the urine volume was increased, the osmotic pressure decreasing below the maximal value observed on a low sodium chloride intake.

McCance and his coworkers[182, 1294, 1303] initially believed that the total amount of osmotically active material claiming excretion determines the minimal urine flow only if the excretion of sodium chloride does not exceed 20 mg/min. (29 gm/day), but, after the administration of sodium chloride, when the concentration of the salt in the urine rises to its maximum, the sodium chloride concentration alone may set the lower limit to water output. Further studies,[987] however, led McCance to abandon this view. When urinary concentrations under conditions of dehydration were compared with those observed after the oral administration of sodium chloride, or after sodium chloride combined with the intravenous administration of sucrose, it was found that the maximal osmotic pressure was reached only at low urine flows. As diuresis increased, the osmotic pressure decreased in a manner suggesting a limitation involving 'a constant amount of osmotic work per unit time.' It is more in keeping with all the facts, however, to believe that the urine flow is independent of the nature of the solute, and that the curve relating urine flow to osmotic pressure merely reflects the reabsorption of an approximately constant amount of water from the isotonic proximal urine.

ing degrees of osmotic diuresis. Actually, the more urea or sodium chloride given, the lower the osmotic concentration of the resulting urine. The limiting osmotic concentration of the urine can, in the present view, be determined only during oliguria, under conditions where the load of water delivered to the distal tubule is less than the maximal rate of reabsorption, and where the only factor limiting the reabsorption of water is the osmotic gradient between the urine and plasma. These conditions have rarely been fulfilled, and indeed it is difficult to see how they can be realized if the concentration of any solute destined for excretion is elevated significantly in the glomerular filtrate.

MAXIMAL SPECIFIC GRAVITY

At best, the specific gravity of the urine is only a blunt index of the degree of concentration because various solutes contribute so differently to the specific gravity. Addis and Shevky,[9,21] in the development of the concentration test named after them, made 94 observations on 75 normal persons, most of whom were medical students, and obtained an average maximal specific gravity of 1.032 ± 0.00281 in a short-period sample collected after 24 hr. of abstinence from water or liquid food. All measurements were above 1.026, and in 95 per cent of the subjects on ordinary diets the specific gravity was 1.028 or above. A specific gravity below 1.026 under the conditions of the Addis-Shevky test may be considered abnormal. In a similar study of Lashmet and Newburg,[1314] all normal subjects concentrated urine to 1.026 or above. The specific gravity of 24 hr. urine samples from 10 normal subjects living under moderate climatic conditions and with no dietary restrictions varied from 1.0079 to 1.0265 because of variable water intake, but after water deprivation for 12 hr. the figure rose to the range of 1.028 to 1.033. The contribution of the various solutes to the specific gravity of these urines was examined by Miller, Price, and Longley.[1111] Statistical analysis reveals that the specific gravity of acid urines collected at random is higher (1.020 ± 0.0047) than that of alkaline urines (1.013 ± 0.0048).[2310] The contribution that individual substances make to the specific gravity of the urine on an equimolecular basis has also been reported by Price *et al.*[1160]

bicarbonate, or of mixtures of the two, in man is about 0.33 M/liter (0.561 osm.), appear to be related to osmotic diuresis. Had the salt been given in larger doses, a lower concentration would have resulted. The fact that a higher electrolyte content (0.50 M/liter) can be obtained if phosphate is mixed with chloride or bicarbonate may be owing to differences in the ionic activity of phosphate salts. Similarly, Gilman and Kidd[781] found that after the ingestion of 1.5 to 24 per cent solutions of sodium chloride in dogs the highest concentration of chloride attained in the urine was approximately 0.31 M (0.527 osm.) and appeared to be little influenced by the rate of urine flow, but, in the light of our present knowledge of osmotic diuresis, a higher concentration would have been expected at lower filtration rates and lower salt loads. In their experiments the maximal concentration of urea was 1.33 osm.

Gamble and his coworkers[741,742] found that rats which were allowed water *ad libitum* and to which various salts and non-electrolytes (sodium, potassium, chloride, bicarbonate, phosphate, sulphate, glucose, galactose, and creatinine) were administered orally excreted urine of essentially constant osmotic pressure whereas if urea was the predominant constituent of the urine more concentrated urine was formed. But the interpretation of these experiments is rendered difficult, first, by the fact that the kidney was not under stress to reabsorb water, and second, by the fact that the water intake may be governed by the mechanism of thirst without reference to the ability of the kidney to excrete a more or less concentrated urine, and third, by differences in the filtration rate. The rat can excrete a more concentrated urine than was observed in any of the foregoing experiments, and it is open to question if that limit is ever reached with water *ad libitum.*

THE LIMITING CONCENTRATION OF THE URINE

The view generally prevalent heretofore, that during osmotic diuresis the urine is maximally concentrated in the sense of having a maximal U/P ratio with respect to urea, sodium chloride, or some other substance, has, for reasons now clear, led only to confusion. To carry out such studies, investigators have administered solutes in varying amounts and thus inadvertently induced vary-

by Rapoport, Brodsky, West, and Mackler,[1610] 1.30 (range 1.2 to 1.4 osm.). More recently, Rapoport, Brodsky, and West [1675] examined the urine of 15 boys, 8 to 15 years of age (26 collection periods of 30 min. each), who were fasting and had received no water for 16 hr. The average urine flow was 0.49 ± 0.03 cc/min. (705 cc/day) per 1 73 sq. m. The average urine osmolarity was 1 182 ± 0.018 osm and the plasma osmolarity 0.304, giving an osmotic U/P ratio of 3 89. With the reservation that allowance must be made for individual variation, we may take the maximal osmotic pressure of the urine in man as 1.4 osm. ($\Delta = 2.50$); setting the concentration of the plasma at 0.33 osm., the maximal osmotic U/P ratio would be 4.2. The osmotic pressure of the urine in a normal dog at various rates of urine flow is illustrated in figure 120.

Data on other species are given in chapter XVII.

RENAL OSMOTIC WORK

Since von Rhorer's calculation in 1905 of the 'osmotic work' required in the urinary concentration of a single component, this problem has been treated by several investigators. More detailed analyses have been undertaken by Borsook and Winegarden [211] and Newburgh [1505, 1509, 1510] The osmotic work of the kidney, thermodynamically conceived, is done in converting the glomerular filtrate into urine The theoretical minimal work is thermodynamically independent of all intermediate steps in the process of urine formation and may be calculated from the rate of urine formation and the U/P ratios of the various urinary constituents, exclusive of substances synthetized by the kidneys, such as ammonia.

The calculation of renal osmotic work in terms of the composition of the final urine, however, necessarily ignores all intermediate steps in urine formation. For example, in the formation of the glomerular filtrate, energy is expended endothermically upon the plasma in concentrating the plasma proteins, this energy being supplied by the heart through the arterial pressure. The greater part of the water of the glomerular filtrate is reabsorbed from the interstitial fluid (after transfer to that point by the tubules) by the osmotic pressure of the postglomerular plasma, an exothermic

Hayman, Shumway, Dumke, and Miller [941] report specific gravities in the urine of female dogs as high as 1.069, with a mode at 1.040 to 1.049, all the urine excreted during 24 hr. of dehydration being used. White and Heinbecker [2108] report the maximal figure in dogs dehydrated for 24 hr. as 1.068, to be compared with 1.039

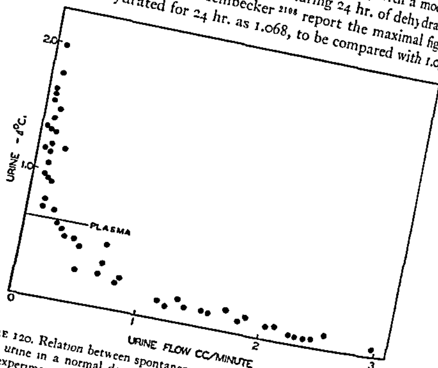


FIGURE 120. Relation between spontaneous urine flow and the osmotic pressure of the urine in a normal dog on a low protein diet. Each point represents a single experimental observation. The line drawn horizontally at $-\Delta = 0.60°$ C. represents the mean of a series of plasma observations obtained during moderate dehydration. These relationships are not fixed in any animal but will vary depending upon variations in filtration rate, food and salt intake. (Shannon [1861])

in diabetes insipidus dogs and 1.040 after total hypophysectomy. The maximal specific gravity in the white rat appears to be about 1.056 (2.0 osm).[959]

MAXIMAL OSMOTIC CONCENTRATION IN MAN

During hydropenia and in the absence of osmotic diuresis, the concentration of the spontaneous urine in man may reach 1.4 osm. The maximal figure indicated by Adolph [27] is about 1.2 osm.; by McCance,[1294] 1.4 osm.; by Gamble and Butler,[737,739] 1.4 osm.; and

by Rapoport, Brodsky, West, and Mackler,[1810] 1.30 (range 1.2 to 1.4 osm.). More recently, Rapoport, Brodsky, and West[1676] examined the urine of 15 boys, 8 to 15 years of age (26 collection periods of 30 min. each), who were fasting and had received no water for 16 hr. The average urine flow was 0.49 ± 0.03 cc/min. (705 cc/day) per 1.73 sq. m. The average urine osmolarity was 1.182 ± 0.018 osm. and the plasma osmolarity 0.304, giving an osmotic U/P ratio of 3.89. With the reservation that allowance must be made for individual variation, we may take the maximal osmotic pressure of the urine in man as 1.4 osm ($\Delta = 2.50$); setting the concentration of the plasma at 0.33 osm., the maximal osmotic U/P ratio would be 4.2. The osmotic pressure of the urine in a normal dog at various rates of urine flow is illustrated in figure 120.

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process in which the plasma proteins are rediluted approximately to their original state. Thus, apart from the separation of a small quantity of water from the plasma as urine water, the net work done upon the plasma proteins is nil. Yet a significant and calculable quantity of cardiac energy has been expended in this cycle, as shown by the decrease in pressure between the glomeruli and the renal vein. The same consideration applies to nearly all the normal constituents of the urine. Some 1100 gm. of sodium chloride, 425 gm. of sodium bicarbonate, 150 gm/day of glucose are filtered, to be reabsorbed almost wholly by the tubules. It has been demonstrated that the reabsorption of all three substances involves an active process requiring the expenditure of energy by the tubules. That water is also ultimately reabsorbed, possibly in great part by passive diffusion, does not abolish the requirement for this energy expenditure. Physiologically, the work represented by the composition of final urine is an almost negligible fraction of the work it is known that the kidney must do in order to make that urine, and the calculation of the so-called minimal thermodynamic work has no more significance. As Borsook and Winegarden [214] pointed out, the work so calculated represents only about 1 per cent of the probable metabolism of the kidney as calculated from the oxygen consumption. This is not to say that the efficiency of the kidney is only 1 per cent; the kidney's efficiency may be very high indeed—it is the thermodynamic approach in terms of final urine that is only 1 per cent efficient.*

For the reasons given above, no great significance can be attached to critical urine volumes representing alleged 'minimal work' [1508, 1510, 1678, 1680] or, in the absence of an accurate fractionation of proximal and distal reabsorption, to estimates of thermodynamic work in these segments.[1681] Minimal thermodynamic work would be done by the kidney only if it excreted 187 liter/day of glomerular filtrate, for then all the energy would be supplied by the heart and the renal work would be zero.

The belief has been expressed from time to time that a high protein diet is injurious to the kidney in renal disease.[14] This question cannot be debated here, but without prejudice to the answer clinically it may be said that the use of a low protein diet cannot be de-

* Mudge *et al.*[1488] have noted the physiological inadequacy of such calculations.

fended on the grounds that it reduces renal work by reducing the quantity of urea requiring excretion. The work so saved represents but a very small fraction of the total work of the kidney, which is not appreciably increased, as judged by the oxygen consumption, by urea or other osmotic diuretics (ch. XXVII).

It is impossible at this time to analyze the significance of the changes in urine composition effected by changes in perfusion pressure, or during urea and Ringer solution diuresis in the perfused kidney, as studied in the painstaking experiments of Eggleton, Pappenheimer, and Winton.[583]

WATER DEPRIVATION AND PHYSIOLOGICAL OLIGURIA

Two types of dehydration may be distinguished That resulting from simple water deprivation is characterized by thirst and oliguria; unless extreme, it does not lead to impairment of the circulation and is completely relieved by the administration of water Dehydration resulting from abnormal salt loss is accompanied in the early stages by reduction of extracellular fluid and plasma volume, and by circulatory insufficiency. It is not necessarily accompanied by thirst and cannot be relieved by the administration of water alone, but requires salt as well as water for correction.[1386 1387, 1499]

It has been noted in chapter III that, although the filtration rate in both the dog and man tends to decrease during dehydration and to increase during excessive hydration, these changes do not appear to be an intrinsic part of the mechanism of water diuresis. Black, McCance, and Young[182] found that dehydration for 3 to 4 days, uncomplicated by starvation but sufficiently severe to make the subjects lose 4 to 7 per cent of the body weight, reduced the filtration rate slightly in 3 subjects (−12 to 28 per cent) and made no difference in a fourth. The renal plasma flow increased in 3 and decreased slightly in 1. At variance with these observations, Kenny[1113] reports that when no free fluid is taken for 2 or 3 days, dehydration leads to hemoconcentration of about 7 or 8 per cent, referable to loss of plasma water without change in the circulating red cell volume. He finds that the filtration rate decreased by 26, 37, and 28 per cent in 3 normal subjects, and the renal plasma flow by 41, 37, and 33 per cent, respectively. The filtration fraction in-

creased markedly in the first and third subjects, but not in the second.

During water deprivation, concentrated urine continues to be formed at a minimal rate—the 'urine obligatoire' of Ambard and Papin.[48] Under conditions avoiding osmotic diuresis, this minimal urine flow is presumably determined by the solutes requiring excretion and by the limiting osmotic concentration of the urine.

The fate of various urinary constituents at low urine flows presents some uncertainties. Chesley[366] reports that when the urine flow falls below 0.35 cc/min., the urea U/B ratio becomes fixed at an average figure of 91.5, and hence the clearance becomes directly proportional to V. Consequently he proposes that in oliguria, 'minimal' urea clearances be calculated in an arbitrary manner comparable to the standard clearance, i.e. by using the observed U/P ratio and assuming $V = 0.35$ cc., disregarding th actual value of V. The average normal minimal clearance so calculated is 32 cc/min. McCance[1294] has pointed out, however, that within the range of Chesley's 'minimal' clearances the urea concentration of the urine can be raised by lowering the sodium chloride output, and hence the constant U/P ratio observed by Chesley may occur only under circumstances where the sodium chloride output, and hence total osmotic pressure, happened to be relatively constant. More generally, under conditions avoiding osmotic diuresis, were only one solute present in the urine, this solute would condition the excretion of water in accordance with the maximal osmotic concentration of the urine; U would be constant, and UV would roughly increase or decrease with P by virtue of changes in V. With the several solutes present in the urine in relatively constant proportions, one would obtain the relationship described by Chesley. In further studies, Chesley[367] reports that when the urine flow falls below 0.35 to 0.5 cc/min., not only urea but phosphate, total nitrogen, and total solids become maximally concentrated. Further reduction in urine flow does not increase the concentration. The plasma clearance of endogenous creatinine shows a linear relation to urine flow, and he suggests that in this oliguric range the filtration rate is reduced and varies directly with urine flow. Under these conditions a constant proportion of filtered water appears to be reabsorbed. Assuming that the endogenous

creatinine clearance reliably reflects the filtration rate, it would follow from the fact that the filtration rate so estimated does increase or decrease with urine flow, that the load of all filtrable substances—urea, chloride, phosphate, total non-protein nitrogen, etc.—also varies with the urine flow because this load varies with the filtration rate; if in various experiments the fraction of the substances reabsorbed by the tubules does not vary greatly, then the residuum (UV) in each case will show direct propotionality to urine flow; i e UV/V will be constant and therefore U will be constant for each substance, as Chesley finds. The essential question is why the filtration rate should vary directly with urine flow. The simplest explanation is that the system operates in reverse; increasing degrees of dehydration lead to greater reduction in filtration rate, and this in turn, by reducing the filtered load of solutes, permits reduction in urine flow in accordance with the limits set by maximal osmotic pressure.

LIFE IN THE DESERT

An interesting series of studies on the physiology of man in the desert was carried out by Adolph and his associates during the war.[32] Observations were made on volunteers in controlled hot rooms as well as under natural desert conditions. Only a few of many interesting points can be recorded here.

At high temperatures, the greater part of the water lost from the body is in the form of sweat. Sweating is, of course, highly variable, depending on temperature, humidity, and physical activity. At a dry-bulb temperature of 100° F., water loss from sweating (including respiratory loss) ranges from 7.2 liter/day when the subject is sitting clothed in good shade, to more than 24 0 liter/day when walking clothed in the sun and carrying a 15 kg. pack, and to 28 0 liter/day when walking nude in the sun without a pack. In contrast, the loss of water in the urine is less variable and comparatively small, being determined by the relatively fixed quantity of urinary solutes.

The mean rate of urine formation among men living in the desert in a warm month was 935 cc/day, as compared with 5905 cc. of fluid ingested. The specific gravity fell largely between the limits of 1.020 and 1.038 and averaged 1.027. It is rare for the

specific gravity of the urine in man to rise above 1.040, the maximal value under the conditions studied being about 1.038, and the mean value at water deficits ranging from 2 to 10 per cent of the initial body weight being 1.033.

Since the urinary water is obligated by urinary solutes, the excretion of urine is reduced only in proportion as the quantity of these substances is reduced. Water cannot be saved by attempting to reduce the urine flow by allowing oneself to become dehydrated. Reduction of urinary solutes, on the other hand, can be accomplished to only a limited extent by modifying the food intake. If nitrogenous intake is much reduced, total food intake is likely to be inadequate, and food reduction of any sort is not recommended in ordinary desert life. Ideally, salt intake might be reduced but, practically, the amount of sweat varies so much from day to day that reduction in salt intake incurs the danger of salt deficiency. In any case, where sweating is profuse the loss of water in the urine is much less important than that lost in sweat.

Under conditions of excessive sweating, and when supplied with water *ad libitum*, men drink only enough to compensate for the minimal urinary and sweat losses; the urine volume is less than the average for men in temperate climates, indicating that men who drink all the water they want remain somewhat dehydrated, presumably because a small water deficit is necessary to stimulate the drinking of the large quantities of water required to compensate for the great loss of sweat. It is in line with this interpretation that men who were deprived of water for 8 to 12 hr. in the hot room excreted the same amount of urine (714 cc.) as those who drank *ad libitum* (709 cc.), i.e. they drank only enough to meet the minimal requirement of total water loss. Some 700 to 900 cc/day of urinary water is usually obligated by excretory products. An output of 500 cc/day is minimal except in near-starvation or when the filtration rate is reduced by severe circulatory disturbances.

The chief expenditure of salt is in the sweat rather than in the urine, despite the fact that acclimatization leads to a reduction in the salt content of the sweat.[464] A few men accumulate considerable crusts of salt upon the skin during a single day's exposure and they characteristically eat excessive quantities, but in all men the salt loss is considerable. Whereas an average of 116 mEq. of

sodium chloride (6.8 gm.) was excreted in the urine at a concentration of 125 mEq/liter, it is estimated that probably 3 or 4 times this amount was metabolized. Taking the average salt content of the body as 165 gm., 10 to 15 per cent of this salt is turned over within 24 hr. No significant change occurs in the chloride content of the plasma either under variable desert conditions or as between individuals freshly arrived or returning to temperate climates. Where men become salt deficient, this deficiency is not necessarily reflected in the chloride content of the plasma, but only by diminished physical performance.[2031]

It is believed that men who suffer near-lethal dehydration cease to form urine, if true, this anuria may reflect circulatory failure which occurs only *in extremis*. Under the field conditions studied by Adolph and his collaborators anuria was not observed. They found no evidence that renal function is impaired by exposure to heat, by moderate dehydration, or by both.

These investigators found that the urea clearance at urine flows ranging from 10 to 50 cc/hr. is practically a linear function of urine flow, as pointed out by Chesley.[386]

Adolph and his colleagues estimate that, at maximal daily shade temperatures of 120°, 110°, 100°, 90°, 80°, and 70° F., a man with no water available can survive 2, 3, 5, 7, 9, and 10 days, respectively, if he is engaging in no exercise at all. If he is walking at night until exhausted and resting thereafter, expected survival is cut to 1, 2, 3, 5, 7, and 7 5 days These figures are, of course, estimates only, because there are no reliable data on the survival or death of men without water on the desert.

The foregoing considerations also apply to survival at sea, except that the length of time required for water deficiency to attain a critical value will depend on air temperature, humidity, wind velocity, protection by clothing or shade, sunburn, and food intake, as well as work in paddling.

The drinking of urine by dehydrated men accomplishes nothing since it affords no free water, nor is drinking sea water advantageous. Taking the maximal osmolar concentration of the urine as 1.4 osm/liter and the concentration of sea water as 1.0 osm/liter, a small part of the water in the latter is theoretically available for the excretion of other urinary constituents. But 500 cc/day of sea

water is about all that can be tolerated, even for a few days, by thirsting men without gastrointestinal disturbances; this would yield at best 143 cc. of free water, and probably less than that amount in many individuals, a quantity too small to maintain a subject in water balance under ideal conditions, much less during exposure to wind and sun. Consumption of larger amounts would lead to diarrhea and more rapid dehydration and only accelerate catastrophe.[737, 1185] Rats survive slightly longer, while losing the same amount of body water, when allowed to drink sea water than when denied all water. But in some individuals the concentration of chloride in the urine (0.60 M) exceeded that in the ingested sea water (0.52 M), a situation that does not obtain in man, the dog, or marine mammals.[30] The only use to which urine and sea water can be put by man is that he can permit them to evaporate from the clothing, thereby cooling the body, as a substitute for a certain amount of sweat. The minimal urine volume is about 10 cc/gm. of protein metabolized; eating raw fish will not ameliorate dehydration since all the water is required to excrete the protein metabolites.[2235]

As Adolph says, there is no cheap substitute for water except to minimize the requirement and conserve whatever is available.

The pathological disturbances characteristic of water or salt deprivation are designated by Adolph as heat stroke, heat exhaustion, dehydration exhaustion, and heat cramp. Heat stroke is accompanied by severe irritability, prostration, and delirium; sweating often diminishes or ceases and the cooling of the body becomes critically deficient, leading to dangerous hyperpyrexia. Heat exhaustion appears more moderately as faintness, vertigo, nausea, vomiting, tachycardia, circulatory inadequacy, and collapse, and appears to be avoided by acclimatization as well as by rest. Dehydration exhaustion is accompanied by vague discomfort and a sense of heat oppression, restlessness, sleepiness, weakness, susceptibility to easy fatigue, hyperpyrexia, tachycardia, tingling of limbs, dyspnea, and circulatory failure. Heat cramps is a syndrome marked by painful spasms of the voluntary muscles following prolonged muscular activity and profuse sweating at high environmental temperatures. The disturbance has been attributed by some investigators solely to loss of salt and hypo-

natremia, but it appears that other factors are involved.[2051, 2216] The depletion of plasma electrolytes is accompanied by the excretion of water, leading to reduction in body fluids and hemoconcentration. The first three disorders are relieved in the early stages by fluids given by mouth or vein and are postponed by rest. It is generally accepted, however, that the ingestion of moderate amounts of salt is both of prophylactic and therapeutic value in heat cramps, whereas drinking water may aggravate the symptoms because of the rapid osmotic dilution of the blood and tissues.[1386, 1387, 2040]

Gamble and Butler,[739] in studies on normal volunteers who underwent prolonged fasting with short periods of thirsting, found that the average maximal concentration of the urine is 1.4 osm. as measured by freezing point depression ($\Delta = 2.6°$ C.). During fasting and dehydration, water is made available by oxidation of body protein, fat, and glycogen and by incidental release from intracellular and extracellular water as tissue is destroyed. Water loss is represented by insensible evaporation (and sweat, if present) and the obligatory urine expenditure at the osmotic ceiling. The minimal renal water required to maintain water equilibrium is represented by the difference between available water and irreducible loss. This figure worked out, in a subject taking 1200 cc/day of water, to be 521 cc.; i.e. he would have remained in water balance on this amount. The addition of 100 gm/day of glucose, by sparing protein, reduced total solute output and hence the renal water requirement to 223 cc/day.

Solute output from an ordinary diet averages 1.2 osm/day, but, with a low protein, low salt, and high carbohydrate diet the output may fall to 200 mosm. The minimal water required for renal excretion under these extreme conditions would be 857 and 143 cc., respectively.

SODIUM CHLORIDE INTOXICATION

Dogs may be killed by the injection of a sufficient quantity of sodium chloride, without change in body water. The increased osmotic pressure of the plasma and interstitial fluid draws water from the tissues and causes intracellular dehydration. Death usually results from respiratory failure. There appears to be no critical lethal concentration of sodium or chloride *per se*.[2236]

POTASSIUM INTOXICATION

Elevation of the serum potassium concentration to 12 mEq/liter or more in dogs leads to death from heart block. Potassium intoxication appears to be the immediate cause of death after bilateral nephrectomy, and in some instances in man it appears to play an important role in death from protracted anuria. Elevated potassium concentration is not the cause of death in chronic glomerulonephritis, the concentration being substantially less than the critical value estimated for man and there being no signs of heart block. This circumstance apparently issues from a relative increase in the potassium clearance in advanced renal disease. However, the administration of potassium salts or potassium-rich food in protracted anuria is dangerous and definitely contraindicated.

EXPERIMENTAL SALT DEFICIENCY

The acute reduction of the salt content of the body in normal man produces a syndrome resembling that caused by adrenal cortical deficiency. This reduction can be accomplished by a low salt diet combined with diuresis and sweating. In studies of experimental salt deficiency by McCance and his coworkers[1289,1291,1293,1299,1300] one subject lost 30 per cent of his body chloride in a few days. His plasma sodium fell from 154 to 139 mEq/liter and the plasma chloride, from 100 to 80 mEq. An equivalent loss in weight occurred, probably attributable largely to reduction of the volume of the extracellular fluid, despite the fact that water was taken *ad libitum*. There were profound muscular weakness, excessive fatigue, mental apathy and confusion, anorexia, nausea, and loss of the sense of taste. There was no acute thirst, despite the loss of body fluid. Slight muscular activity produced cramps, and any muscle suddenly brought into action was liable to spasm, even the muscles of the chest and cheeks.

The total picture in salt deficiency is that the body is forced to compromise between the maintenance of the total base (osmotic pressure) of the plasma and the maintenance of extracellular fluid and blood volume; the former takes precedence over the latter and reduction of extracellular fluid and blood volume, with an in-

crease in hemoglobin and plasma protein, occurs before there is marked depletion of total base

In McCance's studies the filtration rate was reduced by 14 to 36 per cent, a change of possibly critical magnitude in respect to glomerular-tubular balance. The urea clearance was decreased out of proportion to the filtration rate, probably because of oliguria, and because of the reduction in the urea clearance the blood urea rose on a constant protein diet

The extracellular fluid was reduced from 28 to 38 per cent, a reduction large enough to account for the loss in weight. There was possibly some loss of cellular electrolyte and nitrogen and a gain in cellular water owing to the reduction in plasma osmotic pressure.* [1292]

The saliva showed a decreased sodium concentration, increased potassium concentration, and no change in chloride. There was a variable reduction or little change in the free and total hydrochloric acid and in the total chloride of gastric juice. Both sodium and chloride concentration decreased in the cerebrospinal fluid A considerable but variable fall occurred in the concentration of sodium chloride in the sweat. It was shown that adaptation to repeated sweating did not contribute to this result.

The renal responses in salt deficiency are markedly changed from the normal Where normally the ingestion of a large quantity of water leads immediately to marked diuresis, in salt depletion the excretion of water may be delayed 12 hr. Whatever the explanation of this delay, it recalls the similar blunting of diuresis in adrenal insufficiency. A second notable feature is the failure of the kidney to excrete bicarbonate during alkalosis induced by overventilation During and after overventilation, the alkalinity of the urine failed to increase, and indeed in several instances decreased (from pH 6 3 to 5.6, and from 5 3 to 5 0). It is as though, in the face of reduction of plasma sodium concentration, the conservation of sodium takes precedence over the maintenance of acid-base balance, and sodium cannot be spared for the excretion of bicarbonate. This phenomenon is also observed in alkalosis induced by

* Salt deficiency in the rabbit produces the same signs of body fluid and renal disorganization as in man.[1321]

prolonged vomiting and in other circumstances that deplete the plasma sodium or reduce the filtration rate. Instances are on record where the urine was acid despite the fact that the plasma bicarbonate was 90 volumes per cent or more. In all such cases, the administration of sodium chloride, by restoring the plasma sodium, promptly leads to renewed excretion of bicarbonate.[2100]

A third notable difference between the normal subject and one suffering from salt deficiency is that overventilation in the latter produces a marked fall in the urea clearance and in the excretion of endogenous creatinine, presumably owing to a comparable decrease in filtration rate. As a result, in part at least, of this decrease in filtration rate, the diuresis and increased sodium and potassium excretion normally induced by overventilation fail to appear and are replaced by a decrease in urine flow and electrolyte clearances. That the reduction in filtration rate is directly attributable to the alkalosis and not to muscular movements involved in overventilation is shown by the fact that the reduction is prevented if the subject breathes a carbon dioxide-air mixture while overventilating.

Chasis, Goldring, Breed, Schreiner, and Bolomey[355] examined the effects of a low salt-rice diet on hospitalized patients with essential hypertension. The filtration rate decreased in 9 out of 10 patients by the end of the second week, the lowest values reached ranging from 42.4 to 83.5 per cent (average 65.3) of the control level. The PAH clearance decreased in 8 out of 10 patients, the lowest values reached ranging from 61.8 to 92.9 per cent (average 79.5) of the control. Tm_{PAH} decreased in 6 out of 10 patients, the lowest values reached ranging from 72.7 to 91.4 per cent (average 81) of the control. The filtration fraction decreased in 6 out of 10 patients, and in 1 it increased. Addition of salt (30 gm/day) to the rice diet caused the filtration rate to return to or approximately to the control level in all 5 patients in whom it was tried, while the PAH clearance returned to the control level in the 2 patients in whom it had been significantly lowered. Tm_{PAH}, however, showed a further decrease in 4 out of 5 patients to whom salt was administered on the rice diet, and in 1 the depressed value remained unchanged. On return to the ward diet, Tm_{PAH} returned to the control value in 2 patients and approximated it in 1.

Weston, Hellman, Escher, and Leiter[2130] also report a reduction in filtration rate and renal plasma flow in hypertensive subjects on a low salt diet. In their observations limitation of protein also led to a reduction in Tm_{PAH}. It appears that a low salt-rice diet decreases filtration rate and renal plasma flow by virtue of the low salt content, the reduction in Tm_{PAH} being related to low protein intake or features of the diet other than salt There is no reason to believe that the reduction in renal function observed in these hypertensive subjects is materially different than would be expected in normal subjects under the same conditions. However, it should be noted that hypertensive subjects are reported to withstand salt deprivation, so far as weight loss is concerned, better than do normal subjects.[1589]

SIMPLE ALKALOSIS OF OVERVENTILATION

Overventilation for periods of 30 to 45 min. in normal subjects increases the alkalinity of the urine, the pH changing between the extremes of 5 1 and 7.6 to 8.0 It also produces a substantial diuresis The mechanism of alkalinization of the urine is not clear. Under these conditions both plasma pCO_2 and bicarbonate are reduced, and increased bicarbonate excretion cannot be explained in terms of the load of bicarbonate delivered to the distal tubule. It is conceivable that the reduced plasma pCO_2 leads to decreased H^+ secretion in the distal tubule, but there is no experimental evidence to support this interpretation.

In the experiments of McCance and Widdowson[1299] on overventilation in normal subjects, the urea clearance was variably decreased, but, since there was no change in the excretion of creatinine, the change in filtration rate was probably not significant. The rate of excretion of sodium was increased by 50 to 200 per cent, that of potassium by 300 to 500 per cent, changes probably referable to altered reabsorption of cations in association with the excretion of bicarbonate in the distal tubule rather than to altered reabsorption in the proximal tubule.

BICARBONATE ALKALOSIS

Contrary to the earlier belief[1526, 1991, 2290] that the administration of sodium bicarbonate over prolonged periods, as in the treatment of

prolonged vomiting and in other circumstances *that deplete the* plasma sodium or reduce the filtration rate. Instances are on record where the urine was acid despite the fact that the plasma bicarbonate was 90 volumes per cent or more. *In all such cases, the* administration of sodium chloride, by restoring the plasma sodium, promptly leads to renewed excretion of bicarbonate.[2100]

A third notable difference between the normal subject and one suffering from salt deficiency is that overventilation in the latter produces a marked fall in the urea clearance and in the excretion *of endogenous creatinine, presumably* owing to a comparable decrease in filtration rate. As a result, in part at least, of this decrease in filtration rate, the diuresis and increased sodium and *potassium excretion normally induced by overventilation fail to* appear and are replaced by a decrease in urine flow and electrolyte clearances. That the reduction in filtration rate is directly attributable to the alkalosis and not to muscular movements involved in overventilation is shown by the fact that the reduction is prevented if the subject breathes a carbon dioxide-air mixture while overventilating.

Chasis, Goldring, Breed, Schreiner, and Bolomey[255] examined the effects of a low salt-rice diet on hospitalized patients with essential hypertension. The filtration rate decreased in 9 out of 10 patients by the end of the second week, the lowest values reached ranging from 42.4 to 83.5 per cent (average 65.3) of the control level. The PAH clearance decreased in 8 out of 10 patients, the lowest values reached ranging from 61.8 to 92.9 per cent (average 79.5) of the control. Tm_{PAH} decreased in 6 out of 10 patients, the lowest values reached ranging from 72.7 to 91.4 per cent (average 81) of the control. The filtration fraction decreased in 6 out of 10 patients, and in 1 it increased. Addition of salt (30 gm/day) to the rice diet caused the filtration rate to return to or approximately to the control level in all 5 patients in whom it was tried, while the PAH clearance returned to the control level in the 2 patients in whom it had been significantly lowered. Tm_{PAH}, however, showed a further decrease in 4 out of 5 patients to whom salt was administered on the rice diet, and in 1 the depressed value remained unchanged. On return to the ward diet, Tm_{PAH} *returned* to the control value in 2 patients and approximated it in 1.

was above a liter per day during the acute episode, indicating that the patient had suffered some loss of concentrating power. The severe reduction in Tm_D indicates tubular injury, which the authors attribute to renal ischemia, though it may have reflected a direct injury of the tubules with reduction in E_D.

In interpreting these results it should be recognized, on the one hand, that the dog responds to very large doses of sodium chloride by rapid excretion while man excretes excess salt very sluggishly (ch xi). If this response to sodium chloride is pertinent to the handling of large doses of bicarbonate, it is wholly unsafe to reason from experiments on dog to man. On the other hand, bicarbonate is frequently administered clinically where there has been prolonged vomiting with dehydration, which itself has an adverse effect upon the kidney; in so far as the bicarbonate ion will entail the obligatory excretion of additional sodium, this salt may only aggravate a vicious cycle In any case, the data strongly indicate that in man bicarbonate is too dangerous a drug for unrestricted use in self-medication.

WATER INTOXICATION

Water intoxication can be induced by the administration of water at rates more rapid than the kidneys can excrete it, or by stimulating the tubular reabsorption of water by the injection of the antidiuretic hormone in conjunction with water administration. The first symptoms involve the central nervous system, which probably suffers excessive hydration Following protracted convulsions, death occurs from cardiac failure.[1749] Alkalosis and loss of chloride by vomiting or accumulation of gastric juice in the stomach appear to play an important part in the reaction.[1954]

In order to produce water intoxication in dogs retention must exceed 60 cc/kg of body weight, the critical value appears to be from 60 to 70 cc Immediate recovery is effected by the intravenous injection of 10 per cent sodium chloride, whereas urea is relatively ineffective, implying that the disturbance is fundamentally one of superhydration of the body tissues.[908] Instances of water intoxication in man are now relatively rare.[973]

peptic ulcer, leads to renal injury, Kirsner and his coworkers [1122, 1123] could find no pathological evidence for this view by administering bicarbonate to dogs, or from observations on subjects habituated to bicarbonate. Tager and Klinghoffer [2038] report a subject in whom administration of 32,000 gm. of sodium bicarbonate in 20 months produced no marked alteration in plasma electrolytes and no decrease in the urea clearance.

However, McCance and Widdowson [1301] reported a marked reduction of the inulin clearance in a subject with uncompensated alkalosis induced by the prolonged administration of sodium bicarbonate.

As a control on the use of alkali in the therapy of black-water fever, incompatible blood transfusion, and crush syndrome, workers in the Army Malaria Research Unit (Oxford) [62] administered 60 grains of sodium bicarbonate and 60 grains of sodium citrate in 1 ounce of water to 2 normal subjects every 2 hr. for 3 days, and to a third subject every 2 hr. for 1 day only. In 1 subject after 24 hr. on this régime the filtration rate had increased from 179 to 277 cc., in a second subject after 76 hr., from 185 to 163, to 198 cc., and in a third after 68 hr., from 113 to 126, to 260 cc. These remarkable increases in filtration rate were not accompanied by a significant change in the renal plasma flow, so that the filtration fraction increased from 27 to 41, from 23 to 34, and from 23 to 46.8 per cent, i.e. to practically maximal values. In the first subject the urea clearance followed the inulin clearance, but in the second it fell markedly (from 84 to 19.3 cc.) with a rise in blood urea from 19 to 62 mg/100 cc, while in the third it remained unchanged. The decrease in urea clearance the authors attribute to tubular injury, and for this and other reasons consider that large doses of alkali should not be administered in conditions where renal failure may supervene.

Sanderson [1767] also examined a patient in alkalosis (plasma CO_2, 130 vol/100 cc.) and dehydration of vomiting following prolonged ingestion of bicarbonate. The inulin clearance was 22 cc., the diodrast clearance, 231 cc., and Tm_D, 17 mg. of iodine (normal 40 to 50). Following cessation of bicarbonate ingestion and therapy with intravenous saline, partial recovery of renal function ensued, these values 6 weeks later being 54, 353, and 38. The urine flow

and 362 cc., diodrast clearance 631 and 525 cc., renal blood flow 970 and 858 cc., filtration fraction 0.196 and 0.208; Tm_D was measured in only 3 patients before and after delivery, 2 showing an increase and 1 a decrease in this value, but in 8 pregnant women this value averaged 45 6 mg. of iodine. C_D/Tm_D averaged 13.7 and 13.3, and C_{IN}/Tm_D averaged 2 67 and 2.28 antepartum and postpartum. The data on pregnant women are so close to normal and to the postpartum figures that the authors conclude that uncomplicated pregnancy has no effect on renal function.

Dill, Isenhour, Cadden, and Schaffer[522] report on 8 pregnant women in the thirty-second to fortieth week of pregnancy. The average inulin clearance was 116 ± 16.9; diodrast clearance, 637 ± 145; renal blood flow, 950 ± 237 cc/min.; filtration fraction, 0 176. Postpartum, these figures were 139 ± 16.1, 630 ± 90.7, 980 ± 186, and 0.234, the change in the filtration fraction being referable to the increase in filtration rate. The figures are so close to each other and to those for non-pregnant controls that they indicate again that pregnancy does not influence renal function

PRE-ECLAMPSIA AND ECLAMPSIA

(SPECIFIC TOXEMIAS OF PREGNANCY)

Eclampsia is a specific disease of pregnant women, of unknown origin. The term eclampsia is reserved for the severer phase marked by convulsions, pre-eclampsia indicating the non-convulsive phase characterized by hypertension, albuminuria, and edema. Patients who have once had eclampsia or pre-eclampsia are more likely to have subsequent toxemia and a higher incidence of stillbirths and abortions than patients who have experienced uncomplicated pregnancies. Generally the toxemia is promptly relieved by uterine evacuation.[286,374] The renal lesion is primarily glomerular, the capillary tuft being bloodless and swollen; there is clumping and fusion of the loops and eventual hyalinization of some tufts Occlusion of the capillaries is brought about by thickening of the basement membrane and swelling of the mesangial cells between the capillaries The changes are of a degenerative rather than inflammatory character; unlike acute glomerulonephritis, the endothelial nuclei are not increased.[115]

CHAPTER XXI

Disturbances of Renal Function in Non-renal Disease

PREGNANCY

Chesley and Chesley [372] reported an average diodrast clearance in 8 normal pregnant women near term of 610 cc., a figure to be compared with their control observations on 9 normal non-pregnant women of 518 cc. The corresponding whole blood figures were 915 and 900 cc.* They concluded that pregnancy has no effect upon the renal blood flow (These whole blood figures are lower than those reported by others, possibly because of technical differences in the clearance procedure.) In view of the fact that anemia *per se* is not accompanied by an increased whole blood flow to the kidney, the plasma flow remaining constant, the difference in these plasma clearances (518 *vs.* 610 cc.) may indicate moderate renal hyperemia in late pregnancy. The endogenous creatinine chromogen/diodrast clearance ratio averaged 0.129 in pregnancy and 0.122 in non-pregnant women.†

Welsh, Wellen, and Taylor [2168] examined 22 women in the twelfth to forty-first week of pregnancy, and re-examined 11 of these postpartum. The average antepartum and postpartum data were: inulin clearance 124 and 116 cc., phenol red clearance 371

* These data are corrected for the effect of oxalate on the hematocrit, made in accordance with a personal communication to the writer.

† The method of determining the chromogen may be responsible for these low ratios.

women who did not have hypertension before pregnancy but in whom hypertension persisted after toxemia, the urea clearance averaged 53.1 and the diodrast clearance 428 cc., the estimated filtration fraction 0.208. The last figures may be compared with those reported by Chesley for 11 women with essential hypertension who had had no pregnancies: the estimated filtration rate averaged 106 and the diodrast clearance 351 cc., the filtration fraction 0.302. Chesley believes that post-toxemic hypertension differs from essential hypertension in showing a lower filtration fraction because of the glomerular lesion. His data also support the suggestion that it is among those women who have a substantially reduced filtration fraction during toxemia that the potential victims of persistent hypertension (7 of 14 patients) are to be sought, those having normal filtration fractions showing a lower incidence (1 of 16 patients) of post-toxemic effects.

In 10 women with pre-eclampsia, Dill *et al.*[622] report an average inulin clearance of 84 ± 35.3, diodrast clearance 680 ± 283, and renal blood flow 905 ± 425 cc., the filtration fraction being 0.167. After delivery these figures were: inulin, 105 ± 38.5; diodrast, 482 ± 179; renal blood flow, 746 ± 193 cc.; filtration fraction, 0.228. Again, as in their group of normal pregnant women, the increase in the filtration fraction is referable to an increase in filtration rate. In 10 pregnant women with essential hypertension (some of whom had had toxemia at one time) examined in the twenty-eighth to forty-first week of pregnancy, the inulin clearance averaged 87 ± 34, the diodrast clearance 515 ± 234 cc., and the filtration fraction 0.228; after delivery these figures were inulin 95 3 ± 31.9, diodrast 464 ± 115, and filtration fraction 0.234. Again, the filtration fraction is reduced in toxemia and elevated in essential hypertension The authors ascribe the reduction of filtration fraction in toxemia to changes in glomerular pressure rather than decreased glomerular permeability. There seems to be no way to distinguish the two factors at the present time, because all renal hemodynamic calculations must assume an unchanged glomerular permeability coefficient, an assumption that is here invalid because of the glomerular lesion. The authors suggest that the same fundamental vascular abnormality is responsible for the

In 21 women with pre-eclampsia and eclampsia, Chesley, Cornell, Chesley, Katz, and Glissen[374] report an average diodrast clearance of 554 cc., endogenous creatinine chromogen clearance of 75.7 cc., and urea clearance of 66.8 cc., the estimated filtration fraction being 0.148; all these figures are close to their control values in normal pregnant women. The authors conclude that the renal blood flow in the mean is not affected, though the variation is greater. Their patients with eclampsia were, however, examined shortly after delivery.

Corcoran and Page[414] report on 28 women during toxemia. Some of these were studied by the phenol red clearance (before the introduction of diodrast for renal blood flow measurement) and the authors have made an appropriate correction to approximate the corresponding diodrast clearance. They divide their subjects into three groups: A (13 cases), those with a low filtration fraction, B (8 cases), those in whom the filtration fraction was increased and, group C (7 cases), those in whom the filtration fraction was in the normal range. In group A, the average approximate renal blood flow was 989 cc., the average filtration fraction 0.135. Seven of the 13 cases were considered severe, with marked proteinuria in every instance, constriction of retinal arterioles in 12, and retinal edema or papilledema in 6. Postpartum, these patients showed an increase in filtration fraction and a decrease in renal blood flow. The authors attribute the reduction in filtration fraction to swelling of the basement membrane of the glomerular capillaries and note that in this group the clinical course of the disease was most severe. Three of these patients developed persistent hypertension. In group B, the average approximate renal blood flow was 688 cc. and the filtration fraction 0.247. Three of these patients had pre-existing essential hypertension and the authors infer that the group as a whole had pre-existing or latent hypertension. In group C, the approximate renal blood flow averaged 853 cc. and the filtration fraction 0.165. These were considered to be instances of mild toxemia.

Chesley[388] reports that, in 7 women with normal blood pressure after toxemia, the urea clearance averaged 58.0 and the diodrast clearance 507 cc., the estimated filtration fraction 0.189. In 15

increased interstitial pressure, or thickening of the basement membrane of the glomerulus.

Those patients in whom hypertension persists could not be distinguished antepartum from those in whom the blood pressure returned to normal after delivery, except perhaps that they showed a greater decrease in C_D/Tm_D on delivery; the antepartum value of this ratio was above the mean normal in 4 out of 5. The authors suggest that, in the permanently hypertensive group, elevation of the filtration fraction, characteristic of essential hypertension, is prevented by some unknown factor that increases renal blood flow so long as pregnancy continues This suggestion is supported in the later study of Wellen, Welsh, Taylor, and Rosenthal,[2162] who find that the renal blood flow, as judged by the C_D/Tm_D ratio, is increased during pregnancy relative to observations made before conception and after delivery, the filtration rate and Tm_D remaining unchanged Supplementary evidence on this point is derived by them from phenol red and inulin clearances. Comparison of results obtained during pregnancy and for an observation period of 1 to 4 years after delivery indicate that pregnancy itself, when uncomplicated by specific toxemia, does not cause any deterioration of renal function in women with essential hypertension or chronic glomerulonephritis.

Dill, Isenhour, Cadden, and Robinson [521] examined 6 pregnant and 9 non-pregnant women who had had a toxemia of pregnancy 1 to 12 years previously but who were considered normal by both clinical and laboratory methods during the interim. In the 6 pregnant women examined antepartum the filtration rate averaged 84.1 cc.; the renal plasma flow, 500 cc.; the renal blood flow, 750 cc.; the filtration fraction, 0.185. Postpartum these figures were 97.9 cc., 394 cc., 690 cc., and 0.225, again showing a slight increase in renal blood flow and decrease in filtration rate during pregnancy.

In the 9 non-pregnant women, the filtration rate averaged 94 cc., the renal plasma flow, 469 cc.; the renal blood flow, 781 cc.; and the filtration fraction, 0.207. The authors conclude that toxemia, even in the absence of other signs, is usually followed by a reduction in renal function, the degree of which increases with time.

hypertensive diseases and for the toxemias of pregnancy and their sequelae, but this broad generalization must be accepted cautiously.

Wellen, Welsh, and Taylor[2161] report on 11 women examined antepartum and postpartum. They compiled data on normal non-pregnant women by combining the observations of Goldring *et al.*[781] on 9 women with further observations of Welsh, Wellen, and Taylor[2168] and refer to these normal values graphically. Relative to their normal statistics, Tm_D was equally distributed above and below the mean in the pre-eclamptic patients; in only 1 did it deviate more than -2σ, and in this patient it returned to normal after delivery. The changes in Tm_D before and after delivery were, with the one exception mentioned, slight and of random sign. The filtration rate was low, relative to postpartum values, and the ratio C_{IN}/Tm_D was below the mean normal value in all but 2 patients (in 1 this ratio was below -2σ). The C_D/Tm_D ratio, on the other hand, was above the mean normal in 8 of the 11 patients, in 2 instances in excess of $+2\sigma$. In 9 patients (including the 8 above) the ratio fell after delivery, in 3 subjects reaching values below -2σ. The filtration fraction was low (0.11 to 0.20) in all antepartum observations. The data indicate a normal or moderately increased renal blood flow antepartum, with a somewhat reduced filtration rate, giving a low normal filtration fraction.

In the group with clinical cure on delivery, the decrease in diodrast clearance and increase in inulin clearance brought these values and the filtration fraction to a normal range. But in 5 patients who were left with persistent hypertension, the decrease in diodrast clearance and the increase in inulin clearance resulted in high filtration fractions (0.288, 0.210, 0.240, 0.266, and 0.267) typical of patients with essential hypertension, though the C_D/Tm_D ratio was below normal in only 1 subject. The authors reject the view that renal ischemia is an essential factor in the production of hypertension in toxemia of pregnancy because in the presence of hypertension the renal plasma flow is normal and supernormal. Without preference, they suggest that the low filtration rate observed in some patients antepartum could be attributed to increased afferent arteriolar tone, renal edema, and

the fetal heart is lost, these changes take place just as if the uterus had been emptied, and delivery of the dead fetus does not alter the clearances, which remain at the normal level. The data do not permit a firm conclusion, but most investigators believe that the reduced urate clearance is sufficient to account for the hyperuricemia. Whether the decrease in urate clearance is entirely attributable to the decrease in filtration rate or involves increased tubular reabsorption is undetermined. A frequent drop in the uric acid/urea clearance ratio points to participation of the latter. (Chesley, pers com.)

The serum sulphate may rise, in many instances of pre-eclampsia, before or out of proportion to the urea [1055] This may be related to the fact that (in the dog, at least) the plasma sulphate level is almost precisely balanced against sulphate Tm through the filtration rate, and any reduction of the latter will be reflected in an increase in plasma concentration, irrespective of urine flow. The urea clearance, on the other hand, is probably more variably affected by urine volume.

There is some evidence that estrogens are causally related to the retention of sodium in pre-eclampsia, since sodium is retained during periods of high estrogen concentration and lost during periods of diminishing hormones [2050]

Large amounts of both VEM and VDM are regularly present in peripheral blood during the period of pre-eclamptic hypertension, sometimes VEM, sometimes VDM predominating. These factors disappear on return of the pressure to normal levels.[1884]

BILATERAL CORTICAL NECROSIS

'Bilateral cortical necrosis' is a pathologic term applied to certain relatively rare cases of anuria of unknown etiology. The condition is characterized by focal cortical necrosis of varying severity and distribution, both kidneys being generally about equally involved. The inner third of the cortex is usually unaffected but, in severer cases, necrosis may extend into the medulla along the columns of Bertin. In the necrotic zone the interlobular arteries, afferent arterioles, and glomerular vessels are dilated and generally obstructed by thrombi variously composed of fibrin, platelets, conglutinated red cells, and amorphous fatty substance. Thrombus

The data are inadequate to establish that the changes in renal function are significant, but they indicate that, whereas uncomplicated pregnancy has no effect on renal function, in pre-eclampsia the filtration rate is reduced (possibly by the glomerular lesion) with at least a corresponding reduction in filtration fraction. The renal plasma flow and the C_D/Tm_D ratio appear to be elevated. In patients who do not develop persistent hypertension, these deviations in function disappear after delivery; in those who do develop persistent hypertension, the functional pattern shifts to that characteristic of essential hypertension, *viz.* a reduction in renal plasma flow and in the C_D/Tm_D ratio, and an elevation to supernormal levels of the filtration fraction. But these changes, which are always relative, may merely express the development of the essential hypertensive pattern. In no way do they imply that altered renal function is related to the genesis of persistent hypertension.

A rise in blood uric acid without nitrogen retention has been stated to be one of the most consistent signs of pre-eclampsia and eclampsia. Schaffer, Dill, and Cadden [1176] reported reduced uric acid clearances in pre-eclampsia (their clearances may have been elevated by the simultaneous administration of diodrast); the inulin and urea clearances were likewise reduced, and the reduction in uric acid clearance was attributed by them to reduction in filtration rate. Pregnancy itself has no effect on this clearance. Bonsnes, Dill, and Dana [209] report the uric acid clearance in normal women, 1 to 8 days postpartum, as 15.4 ± 3.2 cc. in one series of 9 subjects and 14.0 ± 2.9 in another series of 11 subjects. Chesley and Williams [370,377] report this value in 10 normal women as 15.7 cc. antepartum and 14.9 postpartum, the uric acid/inulin clearance ratios averaging 0.122 and 0.117, respectively. In pre-eclampsia the clearances were 7.8 antepartum and 15.4 postpartum and the clearance ratios 0.081 and 0.137 respectively. Bonsnes and Stander [210] find that the 24 hr. uric acid clearance is generally lower (6.4 cc.) during active pre-eclampsia than during the postpartum or early puerperium period (10.4 cc.), paralleling a reduction in the urea clearance (42 and 55 cc. respectively). The normal 24 hr. uric acid clearance in pregnant and non-pregnant women averages about 12 cc., the urea clearance 63 cc. If

the body. The blood thus made available in the males amounts to some 500 cc/min.

On the average, the inulin clearance was reduced (to 89 cc. in males and 107 cc. in females; normal, 127 and 118, respectively) but in some subjects this function was normal. The filtration fraction was low or low normal. Renal blood flow and filtration rate returned to normal as the hematocrit increased under therapy.

Diodrast Tm was depressed by 22.5 per cent in females and 39 per cent in males. Glucose Tm fell within the normal range in 6 out of 7 patients studied; in the exception, who had diabetes mellitus, it was low In 2 patients Tm_D improved under therapy, the others showing no significant change.

Bradley and Bradley suggest that the edema of chronic anemia, which is unrelated to decreased oncotic pressure or increased venous pressure, may be attributable to the reduced filtration rate, which may fall below 80 cc, and this may also account for reduction in the urea clearance and the development of azotemia in some patients They also comment on the fact that this marked degree of renal ischemia is not accompanied by hypertension, and pre-existing hypertension remains unchanged in chronic anemia Reduction in whole blood flow rather than plasma flow is also indicated in 2 of 3 subjects reported by Aas and Blegen.[2] Restoration of red cell volume effected a large increase in blood flow with no increase in plasma flow. The hyposthenuria observed in some patients with pernicious anemia is apparently not attributable to anoxia of the renal tubules, since concentrating power in dogs is not impaired when the hemoglobin is kept at low levels for one or two months by repeated bleeding.[911]

HEMATEMESIS

Stevens, Schiff, Lublin, and Garber [2001] report that the urea, inulin, and phenol red clearances may be either normal or reduced in the presence of the increased blood urea concentration that follows hematemesis. The reduction in the urea clearance is insufficient to account for the elevation of blood urea and persists in spite of the return of the blood urea to normal The intragastric administration of 2 liters of blood had no effect on renal function.

formation appears to be secondary to renal ischemia, which may be of neural or humoral origin. The condition occurs most frequently in the last trimester of pregnancy and in association with some catastrophic complication. Some investigators believe that, with rare exceptions, true bilateral cortical necrosis is confined to this circumstance and represents one of the toxemias of pregnancy. However, the disease is not to be identified with eclampsia and an entirely similar lesion may occur in males.[115] Others, however, do not distinguish so firmly between the lesion in pregnancy and the bilateral focal ischemic atrophy observed in lupus erythematosus disseminatus, scleroderma, rheumatic fever, periarteritis nodosa, septic abortion, staphylococcus bacteremia, and other conditions giving rise to embolic phenomena in the kidneys and other organs. It is said that treatment is of no avail, and some writers have considered the condition as invariably fatal. However, it is obviously impossible to assert that the same causes and processes underlying those fatal instances of protracted anuria, which at autopsy are identified as 'bilateral cortical necrosis,' may not be present in non-fatal cases where partial recovery of renal function occurs.[51,44,134,323 649,1685]

CHRONIC ANEMIA

Bradley and Bradley[236] have reported on 15 patients with severe chronic anemia (pernicious anemia in relapse, paroxysmal nocturnal hemoglobinuria, duodenal hemorrhage, hemorrhoids, iron deficiency, and lymphatic leukemia). Regardless of etiology, the most striking functional alteration is that the renal plasma flow is only slightly reduced, but the renal blood flow, because of the low hematocrit, is markedly reduced. Thus the diodrast clearance was decreased in males to 522 cc., or by 20 per cent from the normal mean of 655 cc., and in females to 534 cc., or by 11 per cent from the normal mean of 600 cc. These figures are in sharp contrast to 654 cc. whole blood flow in males (normal 1166 cc.), or a 44 per cent reduction, and 673 cc. in females (normal 940 cc.), or a 28 per cent reduction. Since the extraction ratio of PAH is not reduced in anemia[2144] and since the mean arterial pressure is not reduced, the data indicate that in anemia, as in shock, etc., renal vasoconstriction occurs in order to divert blood to other parts of

tients with diabetes mellitus and found Tm_G values in the low normal range. It is probably safe to say that the kidneys are in no way involved in its pathogenesis. Overload of glucose in the proximal tubules leads, however, to osmotic diuresis and polyuria, and some disturbance of salt and water balance is to be expected from this osmotic diuresis. The disturbance of acid-base balance represents primarily a metabolic rather than a renal acidosis.

Despite a marked rise in plasma glucose sufficient to produce frank glucuresis in normal subjects, the urine in some diabetic patients may be almost glucose free, this may reflect a reduction in filtration rate associated with dehydration, which in uncontrolled diabetes can be extreme. An equally important consideration, however, is that, in some elderly patients with a long history of disease, a deposit of hyalin material is formed between the glomerular capillary loops, all or most of the glomeruli being involved to some degree and a few to the extent of almost complete obliteration. This condition, called intercapillary glomerulosclerosis by Kimmelstiel and Wilson, who first described it in 1936, increases in frequency with age, and it is occasionally seen in senile nondiabetics. It is frequently accompanied by massive proteinuria, edema, azotemia, arteriosclerotic hypertension, and other signs of vascular sclerosis.[1380, 1727] A similar lesion has been produced in dogs with experimental pituitary diabetes,[1253] and in rats with alloxan diabetes.[1381]

Hogeman[1025] reports that, in 12 patients with uncomplicated diabetes, renal function did not deviate significantly from his normal controls; the mean inulin clearance was 117 ± 15.4 cc., diodrast clearance 395 ± 68.3 cc.,* and filtration fraction 0.300 ± 0.02. In 12 patients with proteinuria, hypertension, and retinitis, these figures were significantly different from his normals, the mean inulin clearance being 59.2 ± 37.1 cc., diodrast clearance 271 ± 135 cc., and filtration fraction 0.206 ± 0.021. The majority, in respect to both filtration rate and renal plasma flow, fell below -3σ. The reduction in filtration fraction is also statistically significant. Hogeman concludes that diabetes mellitus *per se* does not necessarily cause any demonstrable disturbance in renal func-

* Hogeman's diodrast clearances are consistently low in comparison with those of other investigators

In a patient in moderate oligemic shock caused by severe alimentary hemorrhage, Black, Powell, and Smith[184] report an inulin clearance of 23 cc. and a diodrast clearance of 50 cc. Seventeen hours after transfusion of 850 cc. of blood these figures were 55 and 116 cc., and 3 months later 89 and 453 cc. Similar though less spectacular changes were observed in a second patient before and after recovery. A third patient on admission, when the blood volume was little if at all reduced, showed an inulin clearance of 177 cc and a diodrast clearance of 505 cc. (filtration fraction, 0.35); 20 hr. after transfusion (1200 cc.) these figures were 158 and 325 cc. (filtration fraction, 0.49), and 5 months later the inulin clearance was 112 cc The reason for this high filtration rate is unknown. The patient was severely anemic (23 per cent cells) but, as Bradley *et al*[236] have shown, this circumstance is not generally accompanied by an increase in filtration rate or filtration fraction. Recognizing that E_D may have been reduced by renal injury, the authors conclude that intestinal hemorrhage with moderate oligemic shock is accompanied by renal ischemia.

Studies showing reduction in the urea and creatinine clearances in hematemesis and in other circumstances involving vomiting or hemorrhage, are reviewed by others.[181, 859]

DIARRHEA

Water loss in diarrhea results in shock and extrarenal azotemia, as does salt and water loss through any other portal. In this instance, however, acidosis is the rule, because alkaline intestinal secretions are discharged in large volume,[738] but it is unlikely that acidosis itself causes renal dysfunction.[2236] Rarely, alkalosis may develop.[469, 740] Dehydration is undoubtedly of prime importance, a fact implicit in the recognition by Latta, more than a hundred years ago, that salt and water replacement is the treatment of choice.

DIABETES MELLITUS AND INTERCAPILLARY GLOMERULOSCLEROSIS

In relation to renal function, diabetes mellitus primarily represents a disturbance of metabolism in which the plasma glucose is elevated to such an extent that the load of filtered glucose delivered to the proximal tubules exceeds Tm_G. Nielson[1327] studied 5 pa-

other factors frequently lead to a reduction in blood pressure; if severe, this hypotension may embarrass renal function.[1297] McCance and Widdowson[1304] examined 5 subjects in diabetic coma and found that the filtration rate was considerably below normal. The urea clearance was excessively low, partly because of the low filtration rate and partly because of severe oliguria. However, the exogenous creatinine clearance in 5 out of 5 patients was less than the inulin clearance, the creatinine/inulin clearance ratio ranging from 0.42 to 0.85, in contrast to the normal ratio of 1.2 to 1.4, indicating back diffusion of creatinine (and possibly inulin) as a result of tubular injury.

The excretion of sodium and chloride is low in diabetic coma, probably because of the disturbance in glomerular-tubular balance. The excretion of ammonia may be unimpaired, however, which is to be expected, since ammonia synthesis by the distal tubules is not primarily dependent on glomerular filtration.

The available data do not exclude tubular impairment as a result of metabolic default in the absence of insulin, or some deleterious influence of ketosis.[829, 917, 1998]

CONGENITAL CYANOTIC HEART DISEASE

Scott and Elliott[1814] have reported studies on 19 patients with congenital circulatory anomalies associated with arterial oxygen unsaturation. They distinguish two groups: in group 1 the patients were younger, somewhat smaller, and had higher hematocrits than the patients in group 2. In group 2, renal function was measured simultaneously with cardiac or renal vein catheterization, conditions conducive to anxiety. The two groups differed only in respect to a lower renal blood flow in group 2.

In group 1 (10 subjects), Tm_{PAH} averaged 71.7 mg., a figure only slightly below normal (79 mg.). Of group 2, 7 subjects gave an average E_{PAH} of 0.87, showing essentially normal extraction. The filtration rate in the entire series ranged from 53 to 176 and averaged 110 cc. The PAH clearance ranged from 150 to 666 cc. and averaged 379 cc., a definitely low figure. The hematocrit was high, as is characteristic in chronic anoxia, averaging 73.4 per cent cells; consequently, the whole blood flow was relatively greater than indicated by the plasma flow, averaging 1625 cc. (1164 cc. is

tion, but in the presence of the Kimmelstiel-Wilson syndrome, renal function is markedly impaired. The reduction in filtration rate probably contributes to the high glucose threshold observed in many elderly diabetics.

Farber, Conan, and Earle [615] report that in 10 diabetic subjects without clear evidence of intercapillary glomerulosclerosis the filtration rate was within normal limits, as were most of the Tm_G values. The C_F/Tm_G ratio, however, was lower than normal, perhaps foreshadowing glomerular involvement. Insulin reduced Tm_G in some normal subjects tested and in all the diabetics, raising the C_F/Tm_G ratio toward normal. In several patients the excretion of glucose actually increased after insulin, despite a decrease in plasma glucose concentration. Studies on electrolyte excretion before and after the administration of glucose, or glucose plus insulin, are also reported.

Corcoran, Taylor, and Page [432] report that in 5 patients with intercapillary glomerulosclerosis the filtration rate ranged from 13 to 82 cc. and the diodrast clearance from 139 to 657 cc. Tm_D was subnormal in all but 1 (58 mg. of iodine), ranging from 11 to 26 mg. of iodine. The filtration fraction was low (0.08 to 0.18), as was the C_{IN}/Tm_D ratio (1.05 to 3.12), but the C_D/Tm_D ratio was high, 18.6 to 36, a circumstance the authors attribute to vicarious clearance. They see the lesion as one of the glomerular capillaries, which obstructs filtration more than perfusion, supplemented by loss of function in whole nephrons.

Hilden [1005] reports that in 7 diabetic patients the thiosulphate clearance ranged from 14 to 75 per cent, and Tm_D from 12 to 88 per cent of normal. The thiosulphate clearance/Tm_D ratio ranged from 1.60 to 3.02. The authors conclude that filtration rate and Tm_D are affected about equally.

Data on the reabsorption of glucose by 3 depancreatized dogs are reported by Govaerts and Muller,[829] but control data are unfortunately lacking.

DIABETIC COMA

Extreme dehydration, ketosis, and acidosis culminate in diabetic coma. If for no other reason, it is to be expected that the filtration rate would be reduced in consequence of reduction in the extracellular fluid volume. In addition, reduction in blood volume and

than 10 per cent in 7, the largest increase being from 1310 to 2100 cc. In only 1 did the blood flow decrease by more than 10 per cent. The filtration rate increased by more than 10 per cent in 5, the largest increase being from 111 to 171 cc., and it fell by more than 10 per cent in only 2. The filtration fraction fell in 6 and increased in 4. These patients, plus 5 additional ones not studied postoperatively, confirm the conclusion that aortic coarctation is generally accompanied by moderate to severe renal ischemia with a rise in filtration fraction, indicative of renal arteriolar spasm.

SICKLE CELL ANEMIA

In 5 children with sickle cell anemia, the thiosulphate clearance was subnormal (50.7 to 94.0 cc.), but in the normal range (121 and 150 cc.) in 2 with sickle cell trait and in 1 (145 cc.) with anemia secondary to uncinariasis.[320]

HEPATIC CIRRHOSIS

Cirrhosis of the liver is a chronic degenerative disease of unknown origin, characterized by profound metabolic disturbances leading to hypoproteinemia and cachexia and by the formation of edema. Unlike the edema of cardiac failure, cirrhotic edema is most marked in the abdominal cavity (ascites), a circumstance generally related to increased capillary pressure in the portal circulation.

Factors that might contribute to edema formation are (1) increased portal capillary pressure, (2) hypoalbuminemia, (3) decreased glomerular filtration rate, (4) increased sodium retention, (5) increased water reabsorption by the renal tubules. Nothing is known about variations in portal capillary pressure in man. Hypoalbuminemia, although contributory, appears to be relatively unimportant, since the continued administration of salt-poor human albumin with restoration of the plasma albumin concentration may fail to induce diuresis, and spontaneous diuresis may occur despite continued hypoalbuminemia.[613, 614] Sodium excretion, with or without increased salt administration, is invariably subnormal, the deficiency is not relieved by restoration of the plasma albumin concentration, but ascites formation can be reduced by restriction of salt intake or by the use of mercurial diuretics to

taken as normal by the authors). This renal blood flow represented a greater than normal fraction of the cardiac output; in 11 subjects the average renal fraction was 0.348, whereas the normal probably does not basally exceed 0.20. (This figure varied from 0.18 to 0.603, and 4 observations above 0.40 may reflect multiple errors in cardiac output and renal clearance determination.) The renal arterial-venous oxygen difference (0.7 to 3.4, average 1.7 cc/100 cc.) was within the normal range, as was the renal oxygen consumption (3.0 to 35.0, average 16.2 cc/min.). The uncorrected filtration fraction ranged from 0.20 to 0.55 and averaged 0.31; the filtration fraction corrected for E_{PAH} in 7 subjects averaged 0.24, a slightly elevated figure.

The authors conclude that, in general, cyanotic patients maintain satisfactory excretory function despite polycythemia and a marked reduction in renal plasma flow. The renal blood flow, in this group with congenital cyanotic heart disease, tended to be elevated above normal (possibly as a compensation for diminished renal plasma flow) by vascular adjustments in the kidney rather than by an increase in cardiac output.

COARCTATION OF THE AORTA

Friedman, Selzer, Rosenblum, McLean, and Picard [714] report that, in 4 male and 2 female patients with aortic coarctation, the renal plasma flow was substantially reduced (average 465 cc., range 445 to 531). The filtration rate, however, was much less affected (average 122 cc., range 119 to 130), giving rise to a markedly elevated filtration fraction (average 0.265, range 0.228 to 0.29).

Aortic coarctation is characteristically accompanied by arterial hypertension which is not attributable to anatomic obstruction of the aorta, the diastolic hypertension is equally evident in the femoral arteries,[1992] and it has been suggested that systemic vasoconstriction is related to the release of a pressor substance from the kidneys. Friedman *et al.* consider that the renal ischemia observed by them may also be attributable to this humoral mechanism.

Genest, Newman, Kattus, Sinclair-Smith, and Genecin [781] report pre- and postoperative data on 12 patients with aortic coarctation. The renal blood flow increased postoperatively by more

companied by a marked increase in filtration rate, renal plasma flow, and Tm_{PAH}. A period of fluid accumulation does not apparently militate against normal renal function after the ascites is controlled and may possibly enhance renal function by some compensatory mechanism.

The hepatic blood flow is also generally reduced in cirrhosis, falling well below the normal values.[232]

HEPATORENAL SYNDROME

A voluminous literature has been written on the so-called 'hepatorenal syndrome.' In the main, two points of view have evolved. One maintains that, following biliary or hepatic surgery, thyroidectomy or extensive gastrointestinal operations, a profound derangement of liver function may result in 'liver death,' a rapidly fatal condition characterized by high fever, coma, and usually shock. If the course is less rapid, renal damage results and death occurs in uremia associated with jaundice and other signs of hepatic failure, the 'hepatorenal syndrome.' The opposing view holds that the liver is not primarily involved, and that the syndrome is attributable in most cases to overwhelming sepsis or to obscure infection. Both agree that the kidneys are damaged by toxins that may be released from the damaged liver or that may accumulate in the blood in the absence of the hepatic route of removal. Unfortunately, there is inadequate information on pathology and cardiovascular, renal, and hepatic function to afford a clear understanding of what is probably a mixed group of physiological disturbances.

Bradley[226] points out that renal and hepatic impairment may appear simultaneously in many conditions (intoxication by a variety of substances such as heavy metals, chloroform, cinchophen, dioxane, diethylene glycol, and carbon tetrachloride), in septicemia, Weil's disease, yellow fever, liver trauma, Waterhouse-Friderichsen syndrome, fever therapy, and profound disorders of both the liver (subacute yellow atrophy) and kidney (pyelonephritis). Moreover, cases of acute diffuse glomerulonephritis or acute interstitial nephritis complicating the course of infection or liver disease associated with jaundice may have been

force the excretion of sodium. Mercurial diuretics may, however, fail to increase the excretion of sodium in some cirrhotic patients, as it fails in some patients with edema of chronic congestive heart failure.

Farnsworth and Krakusin [622] report low filtration rate and renal plasma flow in 2 patients in the edematous stage of cirrhosis.

Patek, Mankin, Colcher, Lowell, and Earle [1581] report that, in 3 patients in the edematous stage, the filtration rate was low (75 cc.) in 1, normal (122 cc.) in a second, and elevated (190 cc.) in a third. The corresponding PAH clearances were 356, 512, and 752 cc. One hour after the injection of 50 gm. of human plasma albumin in 0.3 M sodium chloride solution, the renal plasma flow increased to 503, 842, and 821 cc., respectively. (The increase was apparently not maximal at this time, and, in view of Cargill's [327] demonstration that, during renal hyperemia induced by albumin in normal subjects, T_{PAH} is decreased below the normal value of 0.92, the increase in total renal plasma flow may have been considerably greater than is indicated by the foregoing data.) Repeated albumin appeared to lead to sustained improvement in renal function, and indeed to marked renal hyperemia. Patek *et al* conclude that ascites formation is not determined solely by the level of the plasma colloid osmotic pressure and suggest that changes in the permeability of the portal vascular bed and in salt and water metabolism are involved.

Leslie, Johnston, and Ralli (pers. com.) find that, among 29 patients in whom ascites had never been present, or not present to a degree requiring paracentesis, renal function was normal or supernormal, the filtration rate ranging from 113 to 376 cc., renal plasma flow from 540 to 1451 cc., and Tm_{PAH} from 65 to 130 mg. In patients who had at some time required paracenteses but at the time of study had no significant ascites, all measurements fell within the normal range: filtration rate, 109 to 172 cc.; renal plasma flow, 592 to 779 cc.; and Tm_{PAH}, 64 to 82 mg. In patients who were rapidly accumulating ascites, all measurements were depressed: filtration rate, 39 to 106 cc.; renal plasma flow, 253 to 440 cc.; and Tm_{PAH}, 32 to 60 mg. Diuresis under therapy with purified liver extract (intraheptol) and multiple vitamins was ac-

solute quantities of protein excreted in these tests were slight, their significance was validated by Chesley and his coworkers by comparison with the simultaneous excretion of endogenous creatinine, *which eliminates faulty urine collections.* As judged by this clearance, the filtration rate decreased in 9 of 11 subjects studied who showed proteinuria, the maximal decrease (to 76 per cent of the control) occurring in the interval 4 to 8 min.

Chesley and his coworkers concluded that, as Starr had suggested, proteinuria is associated with renal vasoconstriction and glomerular ischemia, proteinuria beginning when the vascular spasm begins to relax at the end of the cold stimulus. However, it may be noted that the proteinuria is almost instantaneous and, in their data, precedes by 2 to 4 min. the maximal indicated change in filtration rate, and it is difficult to believe that so short a period of ischemia would have this effect. Moreover, the studies of Talso, Crosley, and Clarke [2044] on normal subjects do not indicate an invariably rapid response in the kidney to the cold pressor test. The problem invites further investigation by the ureteral catheterization method

POSTURAL PROTEINURIA

Intermittent proteinuria occurs in about three-fourths of youths,* one-third of young men, and one-tenth of old men,[291] during appropriate circumstances chiefly related to posture. The critical factor is the erect, extreme lordotic position. During the proteinuria there is a marked reduction in urine flow and the appearance of large numbers of renal epithelial cells and casts in the urinary sediment, a small increase in red blood cell count occurs inconstantly and congo red escapes into the urine.[1760] In a few subjects protein has been reported as coming from one kidney only.[1681, 2282]

Medes and Berglund [1427] determined the creatinine clearance in normal subjects and in subjects with mild and extreme lordotic proteinuria, during 30 min. of recumbency. The rates were 171 ± 4 cc., 158 ± 5 cc., and 155 ± 7 cc. in these three groups. During

* In 22,000 presumably healthy young men the incidence of proteinuria in single urine samples collected on a day free from undue physical activity was only 1.7 per cent [2164]

reported as cases of hepatorenal syndrome. The terms appear to embrace a large group of diverse entities and may be used only in a descriptive clinical sense.

PROTEINURIA ASSOCIATED WITH TRANSIENT RENAL ISCHEMIA

Many circumstances that are accompanied by severe vasomotor reactions frequently cause the transient excretion of small quantities of protein in subjects who show no evidence of renal disease. Among such circumstances are exposure of the whole body, or even of an arm or leg, to cold water, the administration of adrenalin and ephedrine, the inhalation of carbon dioxide, hemorrhage, and *excitement. It has been generally argued, on the basis of Starr's*[1932] demonstration of the relation of proteinuria to vasomotor responses, that the excretion of protein is attributable to ischemia and increased permeability of some of the glomeruli, though this *explanation is not fully established.*

Chesley, Markowitz, and Wetchler[375] tested a number of women ranging from the third month of pregnancy to the third month after delivery, some with and some without toxemia. One-third of the group had no proteinuria prior to the test, while the rest had some degree of proteinuria ranging from faint traces to 5 gm/liter. While urine was being collected by ureteral catheterization, one hand was immersed in ice water for 1 min. As a result of this procedure, systemic vascular constriction, as indicated by the arterial pressor response, appears and disappears within 2 min Among those subjects who were not excreting protein normally, proteinuria occurred consistently in all who showed blood pressure rises of more than 16/16 mm. Hg, i.e. whose vasomotor response was fairly severe, whereas, of 24 subjects in whom proteinuria did not occur, in only 2 did the blood pressure rise exceed these figures. Protein excretion appears at a maximal rate in the interval 2 to 4 min after the application of the stimulus and thereafter *the rate of excretion diminishes, returning to or near control* levels within 14 min. Allowing for a 2 to 3 min. first appearance time, the excretion of protein must be initiated almost instantly. The right and left kidney usually reacted similarly, though in a few cases proteinuria occurred on only one side. Proteinuria did not correlate with changes in pulse pressure. Although the ab-

MARCH HEMOGLOBINURIA

March hemoglobinuria designates a syndrome associated with exercise and ranging in severity from mild albuminuria without hemoglobinuria or subjective symptoms, to heavy hemoglobinuria and proteinuria preceded by temporarily disabling backache and weakness. The syndrome is so named because it was first observed in an active soldier. The disease is benign, appearing predominantly in young men engaging in certain types of physical exercise, and disappears later in life. The element of lordotic posture is believed to be an important etiological factor, as in postural proteinuria, but there is a suggestion that attacks in some individuals can be abolished by the administration of vitamin C.[654]

PERIARTERITIS NODOSA

This is a relatively rare, necrotizing, vascular disease affecting medium-sized and small arteries and arterioles, usually in several organs. The kidneys are involved in about 80 per cent of the cases, the renal lesion leading to hematuria and albuminuria, renal infarcts, and fibrosis. Death in uremia is common.[875,479,1072] The etiology is unknown but it is possibly a manifestation of an anaphylactic type of hypersensitivity.[479] Clinical and experimental data indicate that it may be induced by drugs (sulfa drugs, antisera, iodine, phenobarbital, thiouracil). Hypertension is commonly present.[2269] No renal function studies are available.

MULTIPLE MYELOMA

Multiple myeloma is a generalized disease of unknown etiology which has its most marked manifestations in the bone marrow, the lesion being characterized by infiltration with so-called 'plasma cells' and local demineralization of the bone.[1239] In a considerable proportion of patients, the disease is accompanied by the excretion of an ill-defined group of proteins known collectively but somewhat inaccurately as Bence-Jones protein. Such protein has a low molecular weight (c.37,000) and is identified by the fact that in slightly acid solution it precipitates in the temperature range of 40 to 60° C. and redissolves on boiling. On cooling, the solution

20 min. of standing in the lordotic position, the rates were, respectively, 167 ± 5 cc., 153 ± 7 cc., and 102 ± 9 cc.; i.e. the creatinine clearance fell only in those with the more severe proteinuria.

Rytand[1160] examined 2 subjects in whom unilateral changes related to posture were revealed roentgenographically and found that the Addis urea excretion ratio and the creatinine clearance fell in the second hour, with the subject erect, to approximately one-half the levels observed with the subject recumbent. In a third, renal function decreased by 20 per cent in the upright position, while in 2 who showed gross anomalies, posture did not affect renal function. Gömöri and Greiner[809] record consistent reduction, averaging 44 per cent, in the creatinine clearance in 6 subjects with orthostatic proteinuria, when assuming the erect position, as compared with a 17 per cent reduction in 7 normal subjects. The former also showed a more marked and more consistent reduction in urine flow.

Bull,[291] who reviews the literature and himself experimentally excluded a number of variables, found that renal function remained essentially unchanged in the recumbent and erect positions, but in the erect lordotic posture the renal plasma flow fell to 33 to 80 per cent of the figure observed in recumbent lordosis, and the filtration rate to 50 to 95 per cent, while the filtration fraction increased. The urine flow was markedly reduced and formed urinary elements of all types were increased in number. In the 2 subjects examined, he obtained protein from both kidneys. From anatomical dissections and various experimental approaches he concludes that in the erect lordotic position, and to a lesser extent in the recumbent lordotic position, the inferior vena cava is compressed against the spine by the posterior surface of the liver, and this induces increased renal venous pressure and passive renal congestion. The compression only occurs when the subject is in a lordotic posture and when the anterior surface of the liver rotates inferiorly. This rotation of the liver normally occurs when the subject is lordotic and is maximal in the erect lordotic position. But it seems probable that some cases of postural proteinuria may be related to distinct anatomical anomalies.[1159]

sometimes by anuria. The renal lesion consists chiefly of focal interstitial inflammation. The glomeruli are not often conspicuously involved. The proximal epithelium is swollen, degenerated, and even necrotic, and commonly obstructed by granular and bile-containing casts. *Leptospirae* can be demonstrated in the cells, lumen, interstitial spaces, and urine.[2011, 2224, 2277]

ERGOSTEROL INTOXICATION

Corcoran, Taylor, and Page[432] report that 2 patients with an illness characterized by malaise, nausea, and vomiting showed evidences of renal impairment, metastatic vascular calcification, and hypercalcemia, which appeared during treatment with a product of the irradiation of ergosterol. Tubular injury was present, as evidenced by low values of Tm_D (10 and 12.6 mg of iodine), but the filtration rate was also low (37 and 48 cc.), as was the renal plasma flow (192 and 285 cc.) and renal blood flow (286 and 407 cc.) The authors speak of the renal disturbance as 'toxic nephrosis.'

HYPERTHYROIDISM AND MYXEDEMA

In 2 patients suffering from hyperthroidism (BMR +83 and +58 per cent), reported by Corcoran and Page,[427] the inulin clearance was 112 and 74, the diodrast clearance rather high (810 and 812 cc.), but Tm_D was in the normal range (35.4 and 40 mg. of iodine). Thyroidectomy had no effect on the clearances and reduced Tm_D by only 10 per cent in 1 patient, while, in the second, thyroidectomy was followed by a moderate decrease in renal plasma flow (812 to 615) and filtration rate (74 to 67 cc.) and a decrease of Tm_D of 10 per cent. In 2 patients reported by Aas and Blegen[2] (BMR +50 and +54 per cent), the inulin clearance was 163 and 121 cc. and the PAH clearance 903 and 927 cc. After therapy with methyl thiouracil, the PAH clearance was reduced in the first patient to 697 cc. but remained unaffected by surgery in the second. In neither did the filtration rate drop.

In 2 patients with myxedema, the renal plasma flow was in the low normal range (509 and 448), the filtration rate definitely low (55 and 33.6 cc.), and Tm_D equally reduced (11.1 and 13.6). Treatment with desiccated thyroid increased the renal plasma flow to 600 and 617, the filtration rate to 101 and 80 cc, and Tm_D

again shows turbidity which disappears on further cooling. The excretion of Bence-Jones protein may amount to more than 10 gm/day over a period of several years.

Multiple myeloma is frequently associated with chronic renal disease which appears to result in part from tubular obstruction by cast formation.[115 1427 1470] Armstrong[61] reports that, in 8 patients, the filtration rate, renal plasma flow, and Tm_{PAH} were depressed to some degree. In 3, Tm_{PAH} was better preserved than the filtration rate. Severity of renal impairment did not correlate with the hematologic or serum protein abnormality, or with the amount or duration of Bence-Jones proteinuria. Armstrong concludes, from these and other data, that tubular obstruction by casts will not adequately explain the impairment of renal function, and he suggests that cast formation may be part of the terminal picture and not the cause of renal failure.

FOCAL GLOMERULONEPHRITIS

Focal glomerular lesions may accompany infection, and particularly staphylococcus, gonococcus, and pneumococcus bacteremia. Focal hyalin and fibrous lesions are frequent in subacute bacterial endocarditis of streptococcus viridans origin. The severity of renal involvement ranges from a few glomeruli or portions of glomerular tufts through the formation of hyalin and fibrous lesions in many glomeruli to a form of focal glomerulonephritis in which glomerulitis involves almost every nephron, leading to renal insufficiency. Some writers believe that this type of glomerulitis is glomerulonephritis. If this proves to be the case, the terms 'focal glomerulonephritis' may be discarded.

Hematuria occurs in the majority of children with subacute bacterial endocarditis and is usually a result of a focal glomerular lesion not associated with renal insufficiency. Among children with subacute bacterial endocarditis who have hematuria, a few prove to have glomerulonephritis and these usually develop renal insufficiency and die in uremia.[221,2113]

WEIL'S DISEASE

Weil's disease, a systemic infection with *Leptospira icterohemorrhagica*, is frequently accompanied by severe renal damage and

CHAPTER XXII

Chronic Congestive Heart Failure

'BACKWARD' AND 'FORWARD' THEORIES

Many diseases of the circulation (arteriosclerosis, essential hypertension, and valvular disease) may terminate in the clinical syndrome designated as chronic congestive heart failure, characterized by dyspnea, orthopnea, cyanosis, increased venous pressure, incapacitating edema, and associated disturbances of function in the liver, kidneys, and other organs. The one invariable sign is enlargement of the heart.

The sequence of events in congestive failure has been the subject of inquiry and debate for over a hundred years. Until the last decade, the most widely held view was roughly as follows: under the principle enunciated by Starling, and long designated as Starling's 'law of the heart,' the energy liberated during contraction increases within limits as the diastolic volume increases (fig. 121). Hence, if for any reason input momentarily exceeds output in either ventricle (and it must be remembered that, considered as a mechanical pump, the heart consists of two independent chambers), the imbalance tends to be physiologically corrected by the resulting distention of the chamber involved; elongation of the muscle fibers makes increased energy available and maintains or increases the stroke volume, thus bringing input and output relative to that chamber back into balance. Under prolonged increased loading, for example such as is imposed on the left ven-

probably both are involved. The author's conclusion appears to be sound, however: tubular function (if we include reduction in renal blood flow) is more severely impaired by prostatic obstruction than is filtration.

PYRIDINE HEPATIC INJURY

Rats fed diets containing pyridine regularly develop acute hepatic necrosis, and animals surviving long enough develop cirrhosis. In some animals, the kidneys show degenerative or necrotic changes. Renal injury was most severe in animals which remained in shock for considerable periods or which survived recurrent episodes of shock. Armstrong [61] infers that the renal injury is, at least in part, owing to renal anoxia associated with shock-induced renal ischemia.

All other circumstances remaining constant, whenever the output of the left ventricle decreases blood tends to drain from the arterial to the venous side of the circulation in consequence of the differential between arterial and venous pressure. This is, of course, the sequence of events during every diastolic interval. Momentarily the quantity of blood on the arterial side decreases and that on the venous side increases The venous pressure rises as blood fills the venous system, and increased venous pressure increases right ventricular filling and output, so that an increased volume of blood is pumped into the pulmonary circuit, leading to increased pulmonary pressure. Increased pulmonary venous pressure in turn increases left ventricular filling and output, and operates to increase the quantity of blood in the arterial system and to diminish the quantity in the venous system.

Precisely the same sequence of events transpires whenever, over a longer period, the output of the left ventricle falls below that of the right. Hemodynamic transmission moves blood from the arterial to the venous system and operates to increase venous pressure. So long as the right ventricle maintains its output equal to the venous return, venous pressure is maintained at normal levels, but blood accumulates in the lungs in excessive quantity, leading to pulmonary congestion with edema, dyspnea, and orthopnea. A steady state is reached when the increase in pulmonary venous pressure suffices by dilatation of the left ventricle to restore left ventricular output to a level equal to the output from the right ventricle.

heart failure as a condition in which the cardiac output is inadequate in relation to the filling load'

It may be noted, however, that the venous return is not accurately reflected by the peripheral venous pressure alone because the flow through the venous system is influenced by venous diameter, even as in the arterial system, and venomotor tone is significantly variable Nor can the venous return be judged by right atrial pressure, any more than the cardiac output can be judged by arteriolar pressure.

It is improper to speak of the 'backward' transmission of pressure in the circulatory system because the heart is the only pump and the pressure imparted to the blood by the heart is (excluding valvular incompetence) only transmitted forward, i e from the arterial to the venous side Every dynamic increment in venous pressure has its origin in the left ventricle, every increment in pulmonary pressure in the right ventricle

tricle in essential hypertension, long-continued increased work induces hypertrophy of the muscle and enlargement of the organ. Similarly, under prolonged increased work the right ventricle may undergo hypertrophy, while in other circumstances both ventricles may hypertrophy in a parallel manner. But in any heart

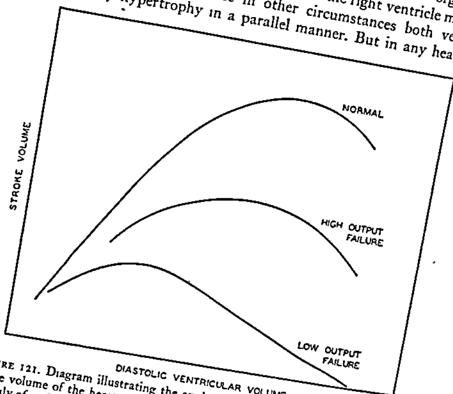


FIGURE 121. Diagram illustrating the application of Starling's law relating the stroke volume of the heart to diastolic ventricular volume One must visualize a family of such curves, since no 1 curve is applicable to all hearts. (Richards [1722])

(normal or enlarged) there is a limit beyond which the myocardium fails, on further dilatation, to respond with increased energy and hence increased stroke volume, as shown in figure 121, and further loading and dilatation lead to reduced stroke volume and to imbalance between input and output.* This point marks the onset of congestive cardiac failure.

* As Huckabee, Casten, and Harrison [1043] remark, 'the *sine qua non* of myocardial failure is therefore to be found not in the cardiac output [with reference to the body's needs] but in the completeness of the cardiac emptying . Pending additional and more complete knowledge it appears justifiable to define

or at least the accuracy of its measurement, has been challenged.[1593]

Starling's views on chronic congestive cardiac failure are frequently misquoted or confused with the interpretations of later investigators. These views are clearly set forth in his article, 'Physiological factors in the causation of dropsy'[1980]

The sequence, as he saw it, consists of:

'Stage 1 —Heart-pump failure; fall of arterial pressure; rise of pressure in the venous trunks near the heart; fall of capillary pressures in the peripheral parts of the body, in the kidneys, and in the intestine; and absorption of fluid by bloodvessels from intestines and peripheral tissues. Stage 2 —Continued absorption from the alimentary canal with diminished excretion from the kidneys, and production of hydraemic plethora with rise of mean systemic pressure. This leads to Stage 3.—Rise of capillary pressure in all dependent parts of the body, capillaries injured by malnutrition, and excessive transudation, leading to dropsy. Stage 4 —The continued hydraemic plethora leads to ever-increasing over-filling of the heart cavities and to ultimate failure of the already incompetent heart.'

It will be noted that Starling invoked diminished excretion by the kidneys to explain the hydremic plethora, and hydremic plethora to explain increased capillary pressure and ultimate failure of the heart.

With the development of improved methods for the measurement of cardiac output it was discovered that, although in the average the cardiac output is reduced in congestive failure, there were notable exceptions in that some persons have a high cardiac output Consequently, certain authors came to believe that a reduced cardiac output is not essential to the production of congestive failure, and that the syndrome involves balancing the cardiac output against the metabolic requirement of the individual; where the cardiac output is antecedently high (cor pulmonale, arteriovenous fistula, thyrotoxicosis, Paget's disease, beri-beri, chronic anemia) cardiac insufficiency will become apparent at a higher level of cardiac output than in a person with antecedently normal output[44, 924, 1722, 1723, 1988, 1989] The difficulty in this view is that there is no method of ascertaining the 'metabolic requirement of the individual.'

After right ventricular failure, a steady state is reached only after peripheral venous pressure has increased to such levels as restore the right ventricular output to a rate equal to venous inflow. At this time peripheral congestion, hypoxia, and edema make their appearance.

Many writers recognize that increased venomotor tone may supplement these hemodynamic factors in contributing to the increased venous pressure.

It is to be accepted that increased capillary pressure (supplemented by capillary hypoxia) leads to increased capillary filtration and to the formation of edema, in the pulmonary circuit only in left ventricular failure, in both the pulmonary and peripheral circuits where both ventricles are incompetent.

The foregoing sequence, here deleted of some subordinate considerations and contradictory opinions, has generally been known as the 'backward' theory of failure, the term 'backward' stemming *from the (here conceived to be inaccurate) concept that the increase* in pulmonary (or alternatively venous) pressure is due to the 'backward' transmission of pressure from the ventricles into *the antecedent reservoirs. (Pressure is never transmitted backwards* in the circulation so long as the atrial-ventricular valves are competent. Every increment in pressure in the venous system has *its genesis in arterial pressure,* i e. *in the left ventricle; in the* pulmonary system, in the right ventricle). The term 'backward' has in part served to distinguish the pure hemodynamic sequence to be expected from myocardial failure from those forms of circulatory insufficiency which have a peripheral origin (hemorrhage, shock, syncope, etc.) and which were usually characterized as 'forward' failure. We prefer to designate the sequence as described above as the 'hemodynamic sequence' in congestive failure.

It is fairly well established that in congestive failure there may be an increase in blood volume,[478, 774, 1436, 1534] sometimes with hypoproteinemia and reduced hematocrit, but generally with normal protein and red cell content (despite the fact that decreased blood volume and hemoconcentration would be expected to issue from this sequence hemodynamically). The mechanism of this increase in blood volume has been a matter of dispute, and even its reality,

(generally below 1.0 gm/day) arrested edema accumulation or caused diuresis, and Futcher and Schroeder[728] demonstrated that mercurial diuretics, long used clinically in the reduction of edema, markedly increased sodium and chloride excretion. They suggested that sodium retention and hence edema formation issued from increased tubular reabsorption of sodium by the renal tubules.

Warren and Stead,[2147] on the basis of the foregoing observations, examined the effects of administering sodium chloride to 2 edema-forming patients, and observed that accumulation of extracellular fluid, as judged by increase in body weight and plasma volume, occurred before there was any increase in venous pressure. They concluded with Starr that the rise in venous pressure issued directly from the increase in plasma volume, which they attributed to the edema itself, i.e. to the expansion of the extracellular fluid. Seeking the cause of the latter, they emphasized the diminished renal excretion of sodium and concluded that the edema of congestive failure results not from capillary pressure but from the failure of the kidney to excrete salt (and secondarily water), for reasons then unknown.

In this view, the renal retention of salt and water leads to expansion of the extracellular fluid and this leads to expansion of the plasma volume, which in turn leads to increased venous pressure. As hemodilution occurs in consequence of the retention of salt and water, reduction of the concentration of plasma proteins serves as a stimulus to protein production, and the plasma protein concentration is restored to or near normal so that the plasma volume and systemic venous pressure tend to be stabilized at supernormal values even though interstitial fluid pressure is not greatly increased.

This view, which emphasizes excessive conservation of sodium by the kidneys as a result of circulatory insufficiency, is sometimes designated the 'forward' theory of failure without due regard to the older usage of this term. It must be noted that, although it shifts emphasis away from the hemodynamic sequence, the sodium retention theory does not abandon basic hemodynamic principles in their entirety. Indeed, even the proponents of the 'forward' theory still envisage the pulmonary edema which accom-

There remains the question whether increased venous pressure should be explained on a pure hemodynamic basis, or as a complex reaction on the part of the body to compensate for cardiac weakness by increasing the heart's filling pressure, a view which had at one time been held by Starling and which has been defended recently by Harrison,[924] Starr,[1983] McMichael,[1882] and Landis, Brown, Fauteux, and Wise.[1206]

Reinterpretation of this problem began in 1940 with Starr and Rawson,[1957] who reported that in a mechanical circulation model 'simulated heart failure' did not cause an increase in 'venous' pressure unless the capacity of the 'circulatory system' was reduced or the 'blood' volume increased simultaneously with weakening of the pump. Starr [1953] further noted that immediately after death the static pressure in the heart and blood vessels was some three times as high in patients dying with cardiac failure as in others without heart disease, and he concluded that the elevation of venous pressure observed in congestive failure is to be attributed largely to a combination of increased blood volume and venoconstriction rather than to 'backward' congestion issuing from cardiac weakness. In other studies, Starr, Jeffers, and Meade [1956] showed that acute and chronic damage to the right ventricle of the dog produces at best only a minimal increase in peripheral venous pressure.

On the basis of these and other studies, Starr emphasized essentially non-cardiac factors (pressure on the vessels by tense, edematous tissue, active constriction of the venous reservoir, increased blood volume accumulating in the most distensible vessels, i.e. in the veins) as of primary importance in the production of venous congestion and thus shifted emphasis away from the hemodynamic sequence.[1981]

SODIUM RETENTION

Meanwhile Schroeder [1803] found that the capacity to excrete so- ium chloride is greatly reduced in patients with congestive heart ailure and persistent edema, an observation which has been con- rmed by Burch and his colleagues, as reported in the *Festschrift or Thomas Addis* [293] and others. Schroeder showed that the re- triction of salt intake to a level below the output in the urine

...lants with

...than 110 cc. requ...

...cc/min. They found...

...henomenon which has been demonstrated in norma... her investigators (ch. xiv), this reaction being exaggerated in some cardiacs so that during exercise the filtration rate, otherwise above the critical level, might fall well below this level, i.e. the renal blood flow was somehow decreased disproportionately whenever the cardiac output proved to be insufficient to meet the demands of the body. In normal subjects the cardiac output increases during exercise, but there is little or no increase in persons with congestive failure, and consequently there develops a large systemic oxygen arterial-... which, Hickam and Cargill [587] suggest, reflects an ... in the tissues. ... leads by some mechanism unknown to ... um retention.*

The renal oxygen arterial-venous difference in congestive failure has been found to be consistently elevated in 9 subjects studied by Breed and Maxwell (unpubl. data), with an average of 2.8 cc/100 cc as compared to their control average of 1.4.

But it seems that the renal ischemia in congestive failure is not generally of such a degree as to impair tubular excretion, and that the PAH clearance used to measure renal blood flow may be accepted at its face value † It has been noted elsewhere (ch. vi) that E_{PAH} in normal subjects averages 0.92 (0.88 to 1.00). In 9 observations on subjects with no renal pathology but in congestive failure Merrill [1035] reported 2 below 0.85 (0.64, 0.63); Warren, Merrill, and Brannon [2145] list 2 determinations as 0.82 and 0.90; Edelman and his coworkers [587] report an average of 0.90 ± 0.037 (0.88 to

...whether the oxygen supply or par... hypoxia do not cause ... in (ch xiv), nor does ... failure (vide infra). ... stration to patients ... rated glucose deriv... ative (ch ...)

panies left ventricular failure as a simple hemodynamic (albeit erroneously 'backward' failure) sequence.[1984, 1888]

RENAL ISCHEMIA

Why the kidneys retain salt and water in congestive failure was then explored by Merrill,[1438, 1439] who showed in patients with persistent edema (i.e. who were in such a state of failure that they required repeated mercurial diuresis to avoid edema on bed rest) that the filtration rate is reduced to one-third or one-half of the normal, the renal plasma flow to an even greater extent, indicating a marked diversion of blood away from the kidneys. Reduction in inulin, phenol red, and urea clearances had previously been recorded by Seymour, Pritchard, Longley, and Hayman;[1442] after compensation effected by digitalis and mercurial diuresis, the phenol red clearance increased in proportion to the cardiac output but the inulin clearance showed no consistent change.

Merrill believed that the decrease in filtration rate reduced the quantity of sodium delivered to the tubules and, assuming normal reabsorptive activity, this circumstance permitted 'unsaturation' of the tubules and almost complete reabsorption of sodium. Since water is invariably retained in the body in proportion to sodium, this reduction in filtration rate led to the retention of both sodium and water. The mechanism by which the renal plasma flow was decreased was unknown; Merrill was unable to correlate this decrease with either increased peripheral venous pressure or increased pressure in the right atrium; on the other hand, the degree of renal ischemia did correlate well with the decrease in cardiac output, and he concluded that the decrease in renal circulation was related to circulatory insufficiency. Here is the only warrant for the use of the term 'forward' failure in this connection; on the widely accepted but unsubstantiated premise that cardiac output is reduced relative to the oxygen requirements of the body (in the majority of patients studied by Merrill, the systemic oxygen arterial-venous difference exceeded the normal value of 4.0 to 6.0 cc/100 cc.), one may liken chronic congestive failure to shock or syncope.

Merrill and Cargill[1440] subsequently reported that, among 25 patients with a filtration rate less than 80 cc/min., all required

which is scarcely beyond $\pm 1\sigma$ from the mean normal value of the inulin clearance/Tm_D ratio of 2.63 ± 0.344.

CONTRARY VIEWS

With the exceptions noted, the observations above are in agreement with Merrill's thesis that in patients with persistent edema the renal blood flow and filtration rates are so low as to demonstrate a reduction in the renal circulation. As a concomitant of this renal ischemia, the filtration rate is reduced and sodium excretion becomes difficult or impossible. The salt retention theory has not escaped criticism, however.

Landis, Brown, Fauteux, and Wise[1205] have emphasized, relative to Starr's experiments on dogs, that he measured the venous pressure at rest; they point out that in the face of even severe cardiac incompetence the venous pressure may increase only during exercise or other conditions where the venous return is increased and the weakened heart overloaded. These investigators demonstrated, moreover, that the intravenous administration of blood or saline to normal dogs in amounts equal to or substantially greater than the normal blood volume does not produce a sustained rise in venous pressure, and they note that conspicuous edema occurs in nephrosis without increase in blood volume or elevation of venous pressure. They suggest that the hypervolemia of failure is a compensatory reaction to many episodes of reduced 'effective' blood volume, and that renal retention of sodium and water as well as overproduction of erythrocytes and plasma proteins fall into this compensatory pattern.

Warren, Merrill, and Stead[2146] reported that 1 hr. after an amount of saline equal to the body weight had been given intravenously to 3 dogs (over a period 6 to 8 hr.) the plasma volume was increased by only 9 per cent in one dog and 4 per cent in a second, while it decreased by 2 per cent in a third; the venous pressure was unchanged in 2 dogs and increased by only 80 mm. saline in the third. Calculations from the recorded weights indicate that at the time these measurements were made the extracellular fluid in these 3 animals had been increased by some 90, 130, and 135 per cent. In view of this demonstration that saline in

0.91) in 10 subjects, and Breed and Maxwell (pers. com.) report an average of 0.93 (0.88 to 0.96) in 4 subjects.

Numerous investigators have confirmed the presence of renal ischemia in most patients with congestive failure. Mokotoff, Ross, and Leiter[1460] report that, in 16 patients with persistent edema at rest, the mannitol clearance averaged 66.8 ± 13.2 and the PAH clearance 191.5 ± 54.4 cc., figures to be compared with 103 ± 12.8 and 627 ± 86.6 cc. in their immediate series of 14 normal or non-failure controls. Briggs, Fowell, Hamilton, Remington, Wheeler, and Winslow[252] report that in 14 uncompensated patients the thiosulphate clearance averaged 70 cc. Aas and Blegen[2] report inulin clearances ranging from 21 to 97 cc. and PAH clearances ranging from 47 to 335 cc. in 4 patients with slight to marked edema; the filtration fraction ranged from 17.2 to 38.4. In 5 patients, with a variety of cardiac impairments but without edema, the inulin clearance ranged from 86 to 109 cc., the PAH clearance from 319 to 538 cc. They confirm the effects of exercise in reducing the renal blood flow. Baldwin, Villarreal, Sirota, Schreiner, and Wesson (pers. com.) report that in 11 uncompensated patients the inulin clearance ranged from 47 to 129 cc., but 4 of them had persistent edema although the filtration rate (92, 97, 98, and 101 cc.) was above Merrill's critical range. In 10 patients in congestive failure due to rheumatic valvular disease, studied by Edelman and his coworkers,[567] the renal plasma flow was reduced about 70 per cent, the filtration rate about 50 per cent. The corrected filtration fraction averaged 0.319 ± 0.074 as compared with their control figure of 0.175 ± 0.033.

In keeping with this interpretation, Weston and Escher[2178] attribute the resistance to mercurial diuresis, which is sometimes shown by patients in congestive failure, to an excessively low filtration rate. They state that, if the filtration rate is increased by aminophylline or hypertonic saline, a marked rise in sodium and water excretion occurs.

Hilden[1008] reports that the thiosulphate clearance in 6 patients in congestive failure ranged from 48 to 83 per cent, while Tm_D ranged from 45 to 98 per cent of normal. The thiosulphate clearance/Tm_D ratio was remarkably constant in the range 2.1 to 2.73,

used digitalis or mercurial therapy to promote compensation, and it would seem that this only demonstrated that compensation can be effected by therapy (mercurials certainly, and digitalis possibly) which specifically promotes sodium excretion regardless of the filtration rate.

The thiosulphate clearances observed by Briggs *et al.* ranged from 20 to 120 cc. (extremely low to low normal) in uncompensated patients, and in only 4 did the clearance increase with compensation under therapy. The mean thiosulphate clearance in 14 uncompensated patients was 70.0 cc. and in 9 compensated patients 81.2 cc They note that the thiocyanate space decreases consistently with compensation, which is to be expected with reduction of edema. However, the thiocyanate space is notoriously variable and unreliable as a measure of extracellular fluid.

Data on cardiac output, oxygen arterial-venous difference, and approximate oxygen saturation of mixed venous blood lead them to emphasize the lowered venous oxygen saturation, 55 per cent in 14 uncompensated patients as compared with 67 per cent in 11 studied after compensation (calculated as venous/arterial contents $\times$ 100), as an important causal factor in the genesis of events in congestive failure and possibly related to reduced sodium clearance. They affirm that edema does not have a hemodynamic origin, since right atrial pressure, though higher than normal, was not consistently higher in the uncompensated than compensated state.

Farnsworth [817] found no correlation between filtration rate and chloride clearance in a patient in congestive failure, the chloride clearance varying from 0.09 to 1.74 cc. at filtration rates of 30 to 64 7 cc., and Farnsworth and Krakusin [821] report a normal filtration rate and renal plasma flow in 1 out of 2 patients.

Kattus, Sinclair-Smith, Genest, and Newman [1093] observed in a young subject with valvular rheumatic heart disease that exercise

mg/min. of sodium at their mean sodium plasma concentration of 3 22 mg/cc. At a plasma level of 25 mg/100 cc. of sodium thiosulphate, a filtration rate of 100 cc would entail the obligatory excretion of 7 mg of sodium, so that the recorded 'sodium clearances' are in great part or in whole thiosulphate clearances, and the changes observed before and after compensation may be related incidentally to variations in the plasma level of this test substance or the rate of its oxidation to sulphate

sufficient quantity to double the extracellular fluid fails to increase either blood volume or venous pressure, one may wonder if some 20 pounds of edema, or an amount sufficient to double the extracellular fluid volume in man, would be associated with an increase in both blood volume and venous pressure to the extent observed in cardiac failure.

Reichsman and Grant[1890] *report that, after the withdrawal of* digitalis in 3 patients with mitral stenosis and auricular fibrillation, the venous pressure clearly rose ahead of the gain in weight and the formation of edema, but this is to be expected hemodynamically and throws no light on the origin of edema because, as Merrill[1439] notes, it is probable that in these patients the rise in venous pressure is coincident with the fall in cardiac output, and the latter may be the effective factor in inducing sodium retention.

Roos and Smith[1742] have shown that acute left ventricular failure, induced in dogs by coronary embolism following the injection of starch into the left ventricular chamber while the aorta is obstructed, leads immediately to pulmonary congestion and increased systemic venous pressure, these effects being augmented if the blood volume is moderately increased. They visualize the sequence in hemodynamic terms, without reference to the present issues.

Borst,[215] reviewing the earlier evidence, rejects the interpretation that reduction in filtration rate represents a disturbance *in* renal function. He favors the view that sodium retention and expansion of blood volume constitute an adaptive reaction, the end effect of which is to increase cardiac output by increasing venous pressure. He marshalls to the support of this interpretation numerous data on other clinical disturbances.

Briggs and his coworkers,[252] studying 10 patients before and after compensation effected by bed rest, low salt diet, diuretics, and digitalis, argue that the sodium clearance improves with compensation independently of the initial magnitude or direction of change in the filtration rate.* *However, these investigators*

* To measure the filtration rate these investigators used sodium thiosulphate, which involves the obligatory excretion of 2 or more equivalents of sodium for every mol of thiosulphate administered. The sodium clearances recorded range from 1 to 3 cc., equivalent in sodium chloride to 9 to 27 gm/day, or 3 to 9

aortic stenosis do not react to hypoxia is not clear. Blegen also records the interesting observation that the renal plasma flow is reduced in subjects with valvular lesions but with no signs of right heart failure.

Threefoot, Gibbons, and Burch [2077] affirm that weight and venous pressure vary directly with sodium and water retention, but were unable to show that either one preceded the other.

Davis and Shock [477] find that, of 6 patients in congestive failure, 4 showed a low sodium clearance despite a normal filtration rate, whereas in the 2 patients who had low filtration rates the sodium clearance was higher than the mean of their 25 normal subjects. These 2 subjects were found, after compensation was effected, to have (arteriosclerotic?) renal disease as judged by loss of concentrating power. (All were receiving saline at 3 cc/min.) This lack of correlation leads them to conclude that reduction of filtration rate is not the primary mechanism for sodium retention. All 4 subjects without renal disease showed a marked or extreme reduction in renal plasma flow, the filtration fraction being correspondingly elevated (0.379 to 0.60). Theophylline ethylene diamine had a more variable effect on renal function in these subjects than in normal subjects. The filtration rate and effective renal plasma flow failed to increase at all in some patients and increased over 100 per cent in others, but there was no consistent change in filtration fraction. Similarly, the sodium clearance increased markedly in some and only slightly in others. The failure of the sodium clearance to increase consistently during a period of increased filtration rate supports this conclusion.

RENAL VENOUS PRESSURE

Winton [2318] showed that increasing venous pressure in the isolated perfused kidney of the dog leads to increased reabsorption of salt and water. Bradley and Bradley [235] observed that, in normal subjects, experimentally increased intra-abdominal pressure, which raises vena caval pressure to 20 mm Hg, increases reabsorption of water, as indicated by increased U/P ratio of inulin or mannitol, an effect which passes off immediately when the pressure is removed; and Bradley, Mudge, Blake, and Alphonse [242] have shown that decrement in water output is associated with an even greater

consistently decreased renal blood flow, filtration rate, and sodium excretion; however, during recovery the filtration rate returned to the control level before the excretion of sodium did. Normal subjects show the same decrease in sodium excretion during exercise, and sometimes to just as marked an extent as did the cardiac patient, but with no change in filtration rate. Hence they conclude that sodium retention is due to increased tubular reabsorption, and is a normal response to exercise and may be expected in the *cardiac as well as in the normal subject, although the response is* exaggerated in cardiac failure. Extending these observations, Sinclair-Smith *et al.*[1902] have challenged the low filtration rate theory on the grounds that mild exercise, which causes sodium retention in normal subjects without significant reduction in filtration rate, invariably causes sodium retention in patients with congestive failure whether the filtration rate decreases or not, and, where the filtration rate is decreased, the sodium retention effect outlasts it. Sodium retention occurred where the endogenous creatinine chromogen clearance had a value of 100 cc. or slightly better, as opposed to Merrill and Cargill's [1140] critical value of 70 cc. Moreover, 1 patient observed over a period of 24 days had a filtration rate (109 cc. by endogenous creatinine chromogen) within normal limits when first studied in the edematous state. Under digitalis, bed rest, and salt restriction, diuresis and decrease of peripheral venous pressure occurred, without change in filtration rate. The renal plasma flow increased, however, from subnormal values (188 cc.) toward normal (417 cc.), decreasing the filtration fraction from 54 to 23 per cent. The authors believe that physical stress, operating by the same mechanism as operates in normal subjects during exercise, increases sodium reabsorption; in more advanced stages or with greater stress, the filtration rate is reduced, causing added retention of sodium by lowering the filtered load.

In a preliminary report Blegen [182] reports that in 8 *normal* subjects he and Aas obtained a significant increase in renal plasma flow with no change in filtration rate while breathing 9.5 per cent oxygen. Excluding patients with aortic stenosis, patients in congestive failure reacted like the normal subjects, and they infer that renal ischemia is not due to hypoxia *per se*. Why patients with

age figure was 22.4 (12.7 to 30.0) mm. Hg; although there is some overlap, the average figure in failure is well within the range which leads in the experiments of Blake *et al.* to sodium and water retention in the dog.

Maxwell *et al.* consider whether the observed increase in renal venous pressure can account for the reduction in renal blood flow and filtration rate in congestive failure, as has been suggested by Seymour *et al.*[1342] Using the equations of Gomez (ch. XVIII) and typical data on renal function they find that in congestive failure the total renal resistance is in the mean increased by 146 per cent, afferent arteriolar resistance by 200 per cent, efferent arteriolar resistance by 110 per cent, and the terminal renal venular resistance by 172 per cent (See also fig. 118.) In relation to overall resistance, the venous component represents only an 18 per cent increase Substituting an elevated (22 mm. Hg) for control (11 mm. Hg) renal venous pressure in calculations on an idealized normal subject, the renal blood flow would be reduced from 1200 to 1032 cc., representing a reduction of only 14 per cent, far less than occurs in congestive failure. They conclude that in failure active constriction of the afferent and efferent arterioles largely accounts for the renal ischemia, the increased renal venous pressure being an additional factor in some cases only, and never the important one. This conclusion is supported by the observation of Merrill that the decrease in renal blood flow does not correlate with the increase in peripheral venous pressure.

Bradley[234] has called attention to the fact that a reduction in filtration rate does not necessarily imply that there is glomerular-tubular imbalance; if some nephrons are inactive, glomerular-tubular balance may be maintained in the residual functional tissue. He notes that although the filtration rate is generally reduced in congestive failure, the increase during compensation is relatively slight,* and patients may live for years with a marked reduction in filtration rate (essential hypertension, some nephritics) with no obvious disturbance in sodium and water balance and no edema. More cogently, perhaps, he emphasizes that left ventricular failure with circulatory insufficiency may develop

* The process of spontaneous compensation, without artificial natriuresis, is one on which there is little information (*vide infra*)

diminution of sodium excretion. These effects are clearly demonstrable in patients with diabetes insipidus and are apparently not referable to changes in ADH secretion. Here, however, the effects of increased renal pelvic (urine) pressure cannot be separated from those of increased renal venous pressure. But Blake, Wegria, Keating, and Ward[188] have found that, if the renal venous pressure is increased into the range of 21 to 27 mm. Hg in laparotomized, anesthetized (pentobarbital) dogs, sodium and water reabsorption by the renal tubules is substantially increased, with no significant change in filtration rate or renal blood flow. The effect is immediate and it is limited to the kidney involved, and hence it is not related to the release of pituitary, adrenal, or other hormones. There was no associated change in Tm_G. Without discounting the role of reduced filtration rate in edema formation, Blake *et al.* argue (incorrectly, the writer believes) that in heart failure the increase in right ventricular pressure at the end of diastole is probably an early if not the first event in failure, and this may lead to an increase in renal venous pressure somewhat ahead of the decrease in cardiac output itself.

Whereas Blake and his coworkers observed no change in renal blood flow or filtration rate in dogs when the renal venous pressure was raised to 27 mm. Hg, Selkurt, Hall, and Spencer[1824] under similar conditions found that these functions decreased proportionally as the perfusion pressure across the renal circuit decreased. An elevation of renal venous pressure of such a magnitude as to decrease the arterial-venous pressure difference across the kidney by about 11 per cent reduced the renal blood flow and filtration rate by 15 per cent, but the authors believe that this is not enough to favor sodium retention, and that mechanisms other than increased renal venous pressure must be operative in congestive failure. Their results are qualitatively in agreement with those of Bradley and Bradley[236] on abdominal compression in man, but the difference in respect to the effects of increased renal venous pressure on filtration rate and renal blood as reported by Selkurt *et al.* and Blake *et al.* remains unexplained.

Maxwell, Breed, and Schwartz[1419] report an average renal venous pressure in 17 normal subjects of 11.7 (10 to 14.6) mm. Hg. In 9 subjects in congestive failure with persistent edema the aver-

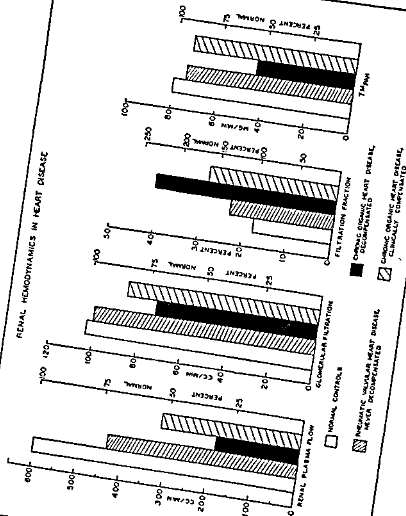


FIGURE 122 The filtration rate, renal plasma flow, filtration fraction, and Tm_{PAH} in normal control subjects and patients with organic heart disease (Heller and Jacobson)

and persist for years with no formation of edema, so long as venous pressure does not rise. He concludes that increased venous pressure and reduction of filtration rate both operate (with perhaps other factors) to produce sodium and water retention; the production of edema will operate to embarrass the already inadequate circulation by further increasing blood volume, venous pressure, and tissue hypoxia, and thus contribute to a vicious cycle. Conversely, it may be noted that hypoxia associated with chronic pulmonary disease or congenital cardiac defects does not lead to edema, so that hypoxia alone does not seem adequate as a stimulus to sodium retention, either by reduction of filtration rate or increased tubular reabsorption. Neither does acute hypoxia reduce the filtration rate in normal subjects or in patients in congestive failure.[2,125]

Heller and Jacobson [950] have studied 3 groups of patients without history of hypertensive disease (figs. 122 and 123):

Group A, 5 patients with rheumatic valvular heart disease but without previous or present evidence of congestive failure.

Group B, 12 patients who had been in congestive failure but who were edema-free and clinically compensated at the time of study. Compensation had been achieved by digitalis, bed rest, and a salt-free diet.

Group C, 13 patients who were in a state of cardiac decompensation at the time of study. Nine had edema varying from a trace to 4+; the other 4 had pulmonary congestion and hepatomegaly.

In those patients in the edematous state at the time of study (group C) the filtration rate ranged from 54 to 105, and averaged 75 ± 20.9 cc.; the renal plasma flow ranged from 90 to 313, and averaged 190 ± 58.2 cc.; the filtration fraction ranged from 0.323 to 0.554, and averaged 0.405 ± 0.083. These figures are to be compared with the authors' data on 8 normal subjects of 103 ± 7.4, 603 ± 84.4, and 0.174 ± 0.023, data which are in reasonable agreement with those summarized in table XII. These patients showed the reduction in both filtration rate and renal plasma flow which characterizes the edematous state in congestive failure.

In those patients who had been in edema but were edema free at the time of study (group B) the filtration rate ranged from 64 to 117 and averaged 86 ± 18.6 cc.; the renal plasma flow ranged

tration rate was close to normal (range 85 to 146, average 101 ± 25.7 cc.) yielding a high filtration fraction (range 0.172 to 0.281, average 0.234 ± 0.04). The demonstration of reduced renal plasma flow in the presence of rheumatic valvular disease but without congestive failure is a highly interesting observation; it should be noted, however, that the renal response differs qualitatively from that in congestive failure, in that the filtration rate is not reduced, and the renal ischemia may have a different mechanism.

In 6 patients studied during the edematous state and after 'compensation' effected by digitalis, bed rest, and salt restriction, the filtration rate increased in only 2 out of 4, and this increase was only 16 and 18 cc, the renal plasma flow, however, increased in all, from an average of 225 to 355 cc., the average filtration fraction falling from 0.481 to 0.319

Hilden's [1008] observations on the reduction of Tm_D in patients with congestive failure have been cited above. Heller and Jacobson find that in edematous patients (group C) Tm_{PAH} is substantially reduced (range 20 9 to 79 7, average 44.2 ± 17.8 mg.) as measured at load/T ratios of 1 5 or more In the 'compensated' group (group B), Tm_{PAH} averaged 71 6 ± 16.5 (range 44 5 to 97.1 mg), and in 2 patients studied before and after compensation this function increased from 36.0 to 65.4, and 53 0 to 78.4 mg., respectively. Tm_{PAH} was essentially normal in the 5 patients with valvular disease (average 73.1 ± 19.2, range 47.9 to 91.0 mg.). These figures may be compared with the authors' average value for Tm_{PAH} in 7 normal subjects of 80.3 ± 20.3 mg (range 60.8 to 105), a figure which agrees excellently with that given in table XII In interpreting the reduction in Tm_{PAH} in the edematous state of congestive failure, the authors dismiss the possibilities of an anatomic reduction of the number of active nephrons, intermittent glomerular occlusion, blockage of 'low pressure' nephrons by elevated venous pressure, and specific tubular injury, in favor of the interpretation that extreme (efferent) arteriolar spasm leads to tubular ischemia. The fact of this reduction is important, but in view of the circumstances that Tm_{PAH} is sensitive to hormonal control from the anterior pituitary, to anoxia and perhaps other factors, the interpretation may perhaps be left open.

from 214 to 444 and averaged 320 ± 86.5 cc.; the filtration fraction ranged from 0.178 to 0.380 and averaged 0.283 ± 0.075. Thus, despite 'compensation' effected by digitalis and sodium restriction, renal ischemia and reduced filtration rate persisted, al-

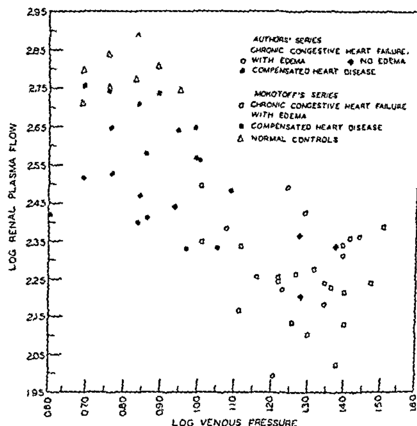


FIGURE 123. Correlation between log renal plasma flow and log venous pressure. Correlation coefficient $r = -0.6969$. P is less than 0.01, indicating a significant degree of correlation (Heller and Jacobson [369])

though renal ischemia was not so severe as in the edematous patients.

As previously recorded by Blegen,[192] Heller and Jacobson found that in 5 patients with rheumatic valvular disease who had never been in congestive failure (group A) the renal plasma flow was reduced (range 338 to 556, average 433 ± 97.2 cc.). (This represents a statistically significant decrease, P less than 0.01.) But the fil-

creased during sleeping hours in all, the average increase being 17 per cent (range +6 to 35). The urine flow increased rather more than the filtration rate (average 25 per cent, range −7 to +50) so that in the mean the inulin U/P ratio fell (average −8 per cent, range −22 to +9); hence there is apparently some diminished water reabsorption superimposed upon increased filtration. The interpretation of this diuresis is rendered difficult, however, by irregularity in water intake and by the possibility of diurnal changes in sodium diuresis. The maximal rates of urine flow were, however, all low (0.38 to 0.69 cc/min.). This inversion of the diurnal cycle is less frequently observed in patients with congestive failure who are not in the edematous state. The data are insufficient to establish whether the change in filtration rate is correlated with increased sodium excretion, which in 3 patients studied increased by an average of 34 per cent. It has been noted (ch. XI) that in normal subjects sodium excretion is generally decreased during sleep, despite a constant filtration rate. It seems likely that here sodium excretion and filtration rate are not directly related.

SPONTANEOUS DIURESIS

Brod and Fejfar [261] report that spontaneous changes in diuresis in uncompensated patients are always secondary to changes in renal plasma flow, increased diuresis is always accompanied by an increase in filtration rate and *vice versa* Such spontaneous changes in diuresis and renal plasma flow are neither preceded nor accompanied by consistent changes in right auricular pressure. They believe that changes in renal plasma flow are independent of changes in cardiac output, and issue from altered distribution of blood in the body. They accept that the retention of salt and water is primarily a result of decreased renal blood flow and filtration rate. Hemodilution is known to occur in normal subjects at night, when the urine flow decreases (ch. XI) and fluid moves from tissues to plasma. Patients in congestive failure and with permanent oliguria, Brod and Fejfar report, show this same nocturnal hemodilution, whereas in patients who show nocturia a transient hemoconcentration occurs shortly after the onset of the nocturnal increase in urine flow.

In group C the average peripheral venous pressure during decompensation was 18.4 ± 5.5 cm. of saline. With clinical recovery this value returned to the normal level of 8.4 ± 2.7 cm. In the 6 patients studied before and after compensation, these figures were 20.2 and 7.6 cm. In both groups the renal plasma flow increased after compensation, but in view of the observations of Maxwell, Breed, and Schwartz it seems unlikely that the decrease in venous pressure could account for the change in renal plasma flow. The correlation coefficient between renal plasma flow and venous pressure among patients with congestive failure was not significantly different from zero, as Merrill [1031] has noted. But if one combines all groups (congestive failure with edema, congestive failure without edema, and compensated heart disease) *the correlation is high* (fig. 123). To the writer, this does not imply that the increase in venous pressure causes the reduction in renal plasma flow, but only that both terms are grossly related to the severity of cardiac insufficiency, however this operates to affect either term.

DIURNAL VARIATIONS

Perera and Berliner [1133] have shown that, both in normal subjects and in patients with chronic congestive failure, the plasma protein concentration, hematocrit, and red cell count vary in a diurnal cycle, being lowest in the early morning after a night's bed rest. Their interpretation is that in the horizontal position extracellular fluid moves into the vascular tree in the manner of an autoinfusion and increases the blood volume. They believe that this phenomenon plays a significant role in the genesis of orthopnea, paroxysmal dyspnea usually occurring during the early morning hours or after prolonged rest.

Brod [268] concluded from endogenous creatinine chromogen clearances that the filtration rate in many subjects with congestive heart failure increases during sleep, in contradistinction to normal subjects where, if any change occurs, it decreases. Baldwin, Villarreal, Schreiner, Sirota, and Wesson (pers. com.), in studies paralleling those which Sirota, Baldwin, and Villarreal [1394] have reported on normal subjects (ch. XI), find in a small number (6) of patients with persistent edema that the inulin clearance in-

nous pressure leads to increased sodium reabsorption and edema, this sequence occurring without a decrease in resting cardiac output, renal plasma flow, filtration rate, or arterial blood pressure. Expansion of the extracellular fluid prevents hemoconcentration and reduction in blood volume despite progressive edema formation. Eventually, anasarca and increased blood volume develop

The ability of the heart with tamponade to increase its output to meet the needs of activity is limited and, with exercise, inadequacy of cardiac output may bring into play 'forward failure' mechanisms (e.g. inordinately decreased renal plasma flow and filtration rate), which contribute to the salt and water retention.

Progressive tamponade leads to further rises in venous pressure, but pre-terminally a critical level is reached; increased venous pressure no longer suffices to maintain adequate resting cardiac output and arterial blood pressure falls. Both renal plasma flow and filtration rate decrease precipitously and this circumstance, with increased renal venous pressure, now operates to accelerate fluid retention and aggravate circulatory embarrassment.

MECHANISM OF RENAL ISCHEMIA

That the renal circulation is susceptible to physiological control is well demonstrated (chs. XI and XIV), but no information is available on how the reduction in renal blood flow in congestive failure is effected. That renal ischemia is not neurogenic in origin seems fairly certain from the observations of Mokotoff and Ross,[1459] who obtained no increase in either renal blood flow or filtration rate in patients subjected to high spinal anesthesia, the blood pressure being maintained by ephedrine, a drug which does not act on the renal arterioles (ch. XIV). It is improbable that the reduction in blood flow is attributable to the continuous secretion of adrenalin, since chronic congestive failure does not present the cardinal symptoms of sympathetic excitation. Since this renal ischemia is apparently not neurogenic and probably not adrenergic in origin, one turns with interest to other possible humoral agents. Merrill, Morrison, and Brannon[1441] very tentatively suggested that it might be mediated by renin, since renal venous blood in 8 out of 11 cardiac patients examined by them showed a significant amount of this agent.

PERIPHERAL VENOUS CONGESTION

Wilkins, Culbertson, Burrows, Tinsley, Judson, and Burnett[2237] have shown that venous congestion of the legs for periods of 10 to 20 min. leads to a transient decrease in filtration rate, renal plasma flow, decreased excretion of sodium, potassium, and chloride, and antidiuresis, and they suggest that peripheral venous congestion resulting from the increased venous pressure in congestive failure may contribute to decreased renal function and sodium excretion. Their studies seem to be equally pertinent to the problem of tourniquet shock (ch. XXIV).

LYMPHATIC DRAINAGE

The role of impaired lymphatic drainage in promoting the edema of chronic congestive failure has not been well defined. In 1876, Gaskell showed that the small lymphatics are connected to the formed elements of the connective tissues by fibrils. As edema forms, distention of the tissues pulls the lymphatic walls apart rather than compressing them. McMaster[1340] has confirmed this observation and finds that, despite wide open lymphatic channels, regions of edema failed to show evidence of lymph flow when locally injected with dye.[1349] The absence of flow is difficult to reconcile with the dilated lymphatics, and he suggests that lymphatic stasis issues from the fact that during dilatation of the vessels the valves are incompetent. Certainly, the efficiency of lymphatic drainage must be taken into account in an already complicated problem.

CARDIAC TAMPONADE

Fishman, Stamler, Katz, Miller, Silber, and Rubenstein[680] have shown that pericarditis with tamponade in dogs causes an increase in peripheral and central venous pressure *pari passu* with increased intrapericardial pressure. The initial rise in peripheral venous pressure occurs without increase in blood volume. The authors accept that this increased venous pressure supports right atrial effective filling pressure and helps to preserve cardiac output. Increased capillary pressure causes extravasation of fluid from the vascular tree, while simultaneously increased renal ve-

secretion of renin or VEM by the kidneys, or of VDM by the liver, has to renal ischemia or other disturbances in congestive failure.

ENDOCRINE FACTORS

The importance of the adrenal cortex in salt and water balance is discussed in chapter XII, where it is noted that certain cortical hormones and related compounds, notably DCA, promote the tubular reabsorption of sodium.

Futcher and Schroeder [728] and Warren and Stead [1161] recognized that changes in endocrine activity might play a role in the retention of sodium in congestive failure, and numerous investigators cited above have had this possibility in mind, but information on the point is lacking because of the absence of reliable tests for adrenal cortical activity. Parrish [1578] reports that the urine of patients in congestive failure shows increased glycogenic activity, and in 4 out of 10 instances there was an increased excretion of corticoids which prolonged the life of adrenalectomized rats. Deming and Luetscher [495] report increased excretion of a DOCA-like compound in congestive failure and nephrosis. Parrish recognizes that increased corticoid excretion may represent a result rather than a cause of the electrolyte disturbances. It will presumably be no easier to disentangle cause and effect in this area than in the sequence of increased venous pressure and edema formation.

INDUCTION OF DIURESIS

Despite the retention of sodium, water is retained to a proportional or greater degree, so that the plasma concentration of sodium is generally low (129.6 to 139.1 as compared with 140.9 to 147.1 mEq/liter in normals),[451, 684] this hyponatremia of course being aggravated by salt restriction and mercurial diuresis.[1378]

It is now recognized that mercurial diuretics promote diuresis by reducing the tubular reabsorption of sodium, probably in the distal tubule. Whether mercury also specifically reduces water reabsorption is not determined (ch. XXVII). It seems probable that, once sodium is excreted, readjustment of water balance is effected through the normal operation of the supraopticohypophysial system.

Alternatively, Mokotoff, Shorr, and their collaborators (pers. com.)[1458] report that VEM was present in large amounts in the renal venous blood of 10 out of 12 patients in congestive failure, and especially those showing a high filtration fraction, in contrast to the presence of only trace amounts in 3 out of 13 control subjects. In such patients the oxygen saturation of renal venous blood was reduced; the mean renal capillary oxygen tension was calculated to be 44 mm. Hg as compared with 62 mm. in the control group, i.e. the renal parenchyma is suffering from significant hypoxia as judged by the oxygen tension which is critical for the aerobic enzyme system which destroys VEM. Although the renal oxygen arterial-venous difference is increased (3.35 ± 1.09 cc/100 cc.) above their normal figure (1.29 ± 0.31 cc/100 cc.), the renal oxygen consumption is somewhat reduced because of a reduced blood flow (12.0 cc/min. as compared with 15.8 cc. in the controls). The critical state of renal hypoxia necessary for the liberation of VEM appears to be reached when the renal blood flow falls below 600 cc/min., or about half the normal. VDM was present in hepatic venous blood samples in 10 of 11 patients in congestive failure, while only 3 of 14 controls showed mild VDM activity. In femoral arterial blood there was a slight preponderance of VEM in 5 failure patients, but 4 showed preponderance of VDM, while a neutral response occurred in 2 failure patients as compared with 13 controls, all of whom showed a neutral reaction. By decreasing the oxygen tension in the inspired air in 2 normal subjects, it was shown that VEM is produced by the kidney after 15 min. of low oxygen, without a change in renal oxygen consumption or oxygen arterial-venous difference. The increase in VDM is significant in view of Myers and Hickam's[1497] demonstration that in congestive failure the hepatic blood flow is reduced to some 60 per cent of normal.

VDM is an antidiuretic substance which apparently acts by increasing the secretion of ADH, and Shorr and his colleagues have suggested that it may play a role in the retention of water in the formation of edema. However, there is no evidence as yet that the retention of water *per se* will lead to the retention of sodium (ch. XI). It remains to be determined what relation, if any, increased

physiologically well grounded, and in the hands of others has not proved superior to sodium restriction alone.[1111]

In the absence of any method of improving the renal circulation and increasing glomerular activity, the therapy of congestive failure must for the time being follow the conventional lines of improving cardiac action by digitalization, coupled with salt restriction and such diuretic measures as promote the excretion of sodium.

Dock has recently raised the question whether our salt intake has become excessive by habituation. He notes [525] that among the great apes, living on seeds, nuts, and fruit, sodium intake rarely exceeds 250 mg. on a 3000 calorie intake; among primitive people in the tropical rain forests it is rarely more than 500 mg/day, and often is much less The average intake for many Americans may exceed 5 gm/day. What significance, if any, this high salt intake has in accelerating the crisis of congestive failure remains concealed, along with many other questions, for future examination.

A concise summary of the evidence bearing on the role of the kidney in chronic congestive heart failure would be as difficult as a final interpretation It will perhaps suffice to emphasize a few outstanding points.

When Starr, Warren, and Stead and Merrill approached a reinterpretation of this problem, no quantitative data were available on the problem of glomerular-tubular balance and sodium excretion, but those data which have become available in the interim (ch. XI) support their emphasis upon the importance of glomerular-tubular balance; the operations of the distal tubule upon some small fraction (perhaps one-eighth) of the filtered sodium determine the retention or excretion of this ion, and hence the overall retention or excretion of salt and water. The writer and his colleagues are prepared to accept that, all other factors remaining constant, a reduction in filtration rate of the order of magnitude suggested by Merrill (to 70 to 80 cc.) will result in persistent sodium retention.

It must be recognized, however, that sodium reabsorption, either distally or proximally, is profoundly influenced by adrenal cortical hormones, ADH, and possibly other factors, a circum-

Xanthine derivatives tend to increase the filtration rate, but their effect in this respect is moderate, transient, and uncertain. Several investigators have presented evidence that, in addition to this hemodynamic effect, the xanthine derivatives, and particularly theophylline, specifically depress sodium reabsorption by the renal tubules (ch. XXVII).

The therapeutic value of digitalis has long been attributed to its cardiac action, but McMichael and Sharpey-Schafer have argued [1353] that it dilates the venous reservoir and in some instances may improve the stroke volume of the heart by reducing ventricular volume into the physiological range of Starling's law. Handley and Telford [903] reaffirm that in dogs this drug decreases the plasma volume, increases the hematocrit and increases the thiocyanate space, the last involving movement of water out of the tissues. They state, however, that there is no evidence that these extracardiac effects are concerned in its therapeutic use. Ferrer and Sokoloff [637] report that morphine and demerol may reduce mercurial diuresis, even though in the absence of a mercurial diuretic, morphine tends to increase natriuresis, presumably by release of ADH.

Earle, Farber, Alexander, and Eichna [564] have some evidence, not conclusive as yet but strongly suggestive, that digoxin also has a specific renal effect in blocking sodium reabsorption, independently of its effects on cardiac output or venous pressure (ch. XXVII). The question may be raised whether compensation under digitalis, as well as under salt restriction and mercurial therapy, throws any light upon the importance of the filtration rate in edema formation.

Water diuresis tends to be blunted in congestive failure, presumably because of the reduced filtration rate, and the effects of prolonged water diuresis on sodium excretion are rather ambiguous even in the normal subject (ch. XI). There is no convincing evidence that water diuresis increases the excretion of sodium either in the normal subject or in the subject in congestive failure. Schemm [1780] has recommended a regime of salt restriction coupled with the administration of very large quantities of water for the reduction of edema. This regime, however, cannot be said to be

part and to ascertain, where possible, the sequence of events, which may differ markedly not only in relation to easily described pathology, but in relation to less easily described physiological circumstances.

The chairman of a recent scientific session facetiously remarked that the current trend was to demonstrate that the heart had nothing to do with congestive heart failure. It may be that the heart is remotely involved in chronic congestive failure but, when the problem is fully resolved, a great deal of non-cardiac physiology will certainly have been added to this chapter.

stance which in part explains the maintenance of salt and water balance in the face of wide changes in filtration rate in health and disease; that, as Blake and his coworkers have shown, a sufficient increase in renal venous pressure can reduce sodium and water excretion; that pure hemodynamic factors contribute to the increase in systemic venous pressure and to the formation of edema; and, most importantly, that the renal ischemia and reduction in filtration rate cannot be attributed to the increase in renal venous pressure alone.

Sometimes it is disadvantageous to look upon physiological reactions in health and disease as teleologically adaptive; they operate as they do because of an infallible sequence of cause and effect. The fact of renal ischemia in the majority of patients in chronic congestive failure is incontrovertible. The reason for this ischemia, and the means by which it is effected, remain mysterious. It is probably not caused by hypoxia *per se*, and apparently not mediated neurogenically. There is no reason at this time to believe that it is an adaptive phenomenon. It may be accepted that the blood volume is increased, but it is not proved that this increase is solely a result of expansion of extracellular fluid volume. Apart from McMaster's demonstration of lymphatic stasis, nothing is known about lymphatic activity in the edematous state.

There are good reasons for believing that the renal circulation and the endocrine control of sodium excretion are normally coordinated in such a manner as to maintain a normal volume of extracellular fluid (which is itself part of the circulatory system, in a broad sense). In chronic congestive heart failure this coordination has broken down. Renal ischemia, perhaps increased sodium reabsorption, certainly sodium and water retention, follow, with the formation of edema, which serves not to increase the blood volume and the venous pressure in order to increase the filling of the heart in an attempt to increase cardiac output, but only to embarrass an already deficient heart and circulatory tree.

Accurate information on the sequence of events will not be obtained by overemphasizing one part of this complex and delicately co-ordinated system to the prejudice of another, but rather by an effort to acquire more precise quantitative information on each

cardiac output in the basal condition does not cover all the exigencies of life but, at least as far as the basal state is concerned, the elevation of pressure may be attributed to increased peripheral resistance. The fact that it is the diastolic pressure which is typically and persistently elevated, implying increased resistance to outflow, supports this conclusion.

The data of Bolomey *et al.* (which include control observations on 6 patients reported by Goldring and Chasis [792]) show an average peripheral resistance of 1160 absolute units in 18 subjects without hypertensive disease; in 19 subjects with hypertensive disease the average figure was 1950 absolute units: i.e. the peripheral resistance was 68 per cent greater than normal.

Since no obstruction exists in the major arteries and the evidence is against any increase in capillary resistance, *the critical physiological change in the vascular tree may be referred to increased tone in the arterioles* which stand intermediately between the larger arterial conduits and the capillaries; these arterioles contribute the larger fraction of the total hemodynamic resistance of the circulatory tree, and in transit through them the arterial blood suffers the greatest decrement in pressure and the greatest expenditure of that energy which is imparted to it by the contraction of the heart (see fig. 53, p. 299). It is by variation in this arteriolar tonus, through neural or humoral mechanisms, that blood is diverted from one organ to another and that the vasomotor reflexes operate to maintain the median pressure in the arterial reservoir. The systolic pressure is hemodynamically related to the stroke volume of the heart and the volume elasticity coefficient of the arterial reservoir; it is elevated in hypertensive disease, with a concomitant increase in pulse pressure, not because of any increase in stroke volume but in part because there is some decrease in the volume elasticity of the arterial tree and in part because of the increased diastolic pressure. The diastolic pressure is hemodynamically related to the 'run-off' or residual pressure in the arterial reservoir at the end of diastole, and it is increased by any circumstance that impedes outflow from the arterial reservoir. Hence the diastolic pressure is the *more significant* in interpreting the hypertensive status of the patient. Although the arterioles in the advanced stages of essential hypertension show medial hy-

CHAPTER XXIII

Essential Hypertension

Various disorders of the cardiovascular system lead to an increase in diastolic or systolic pressure, or both, but the most frequent and the most mysterious is the condition known as essential hypertension, the etiology of which is unknown. This disease is characterized by elevation of both diastolic and systolic pressure, elevation of the diastolic being a *sine qua non* and serving to distinguish essential hypertension from arterial sclerosis, aortic insufficiency, arteriovenous fistulas, hyperthyroidism, and other conditions wherein only the systolic pressure typically rises above normal limits. The upper limits of 'normal' blood pressure are difficult to define, but as an arbitrary basis these limits are widely taken as 90 mm. Hg diastolic and 140 mm. Hg systolic pressure.

It is now well established that the basal cardiac output is not increased in essential hypertension.[249,785] In a recent study by Bolomey, Michie, Michie, Breed, Schreiner, and Lauson,[107] the cardiac index as determined by the direct Fick method in 19 hypertensive subjects averaged 3.97 liter/min. per sq. m., in 18 nonhypertensive subjects, 4.07 liter/min. per sq. m. (Both figures are probably elevated slightly by the multiple procedures of cardiac output and clearance determinations, as pointed out on page 552.) The mean arterial pressure averaged 145 mm. Hg in the hypertensive subjects, and 92 mm. in the controls. Admittedly, the

factory, heart disease in all forms is the cause of death in nearly one-half of the adult population; in the category of heart disease, the sequelae of essential hypertension appear to account for about half of these deaths, or some 25 per cent of the total adult figure.

In about two-thirds of victims of hypertensive disease,[115] heart failure in one form or another is the immediate cause of death. In some, death is caused by coronary thrombosis; in others, the heart, continuously faced with the expulsion of blood against an elevated pressure, undergoes hypertrophy and ultimately dilates beyond compensatory limits, precipitating congestive heart failure. It is to be noted that despite left ventricular failure (and elevated pulmonary arterial pressure) right ventricular pressure and systemic venous pressure are not increased, and edema is absent in hypertensive heart disease unless and until congestive failure supervenes in consequence of right ventricular failure.

In some 10 to 20 per cent of cases, death is due to catastrophic cerebral hemorrhage or thrombosis, precipitated by pathologic changes in the cerebral arteries. Disturbances of the cerebral circulation are often evident early in the disease; headache is one of the earliest and most frequent symptoms, and transient episodes of sensory and motor disturbances, aphasia, or amaurosis are frequent. In the eye the arteriolar changes lead to a reduction in the caliber of the retinal vessels, venous obstruction, hemorrhages, and retinal edema, often with serious impairment of vision.

Death ensues from specific renal damage in about 10 per cent of subjects, although the kidneys appear to be neither more nor less fortunate in escaping the ravages of the disease in all subjects. In some 12 per cent death occurs from causes unrelated to hypertensive disease.

The increase in mean arterial pressure offsets the increased arteriolar resistance, with the result that there is a normal blood flow everywhere throughout the body; every major circuit has been examined in patients with essential hypertension without eliciting any evidence of selectivity for any particular vascular circuit in its early stages. Whether the heart, the brain, or the kidneys will prove to be the weak point in physiological endurance cannot be predicted before the organic derangement becomes an overt fact. But, because of enhanced arteriolar tonus and possibly because of

pertrophy and intimal hyperplasia which tend to narrow the lumen,[114] these pathological changes are not responsible for the increase in peripheral resistance, which has a functional origin. Hypertension of long duration may be associated with little if any visible vascular damage,[2042] while the vascular disease may persist and progress even after sympathectomy has reduced blood pressure.[795, 868, 1951, 1952]

The raw statistics indicate that the incidence of essential hypertension, quite low before the age of 20, rises rapidly thereafter until at the age of 40 approximately 25 per cent of the population are affected, this figure increasing to 60 per cent or more in elderly persons. One extreme estimate implies that one-half of the male population of the United States and 60 per cent of the female population 40 years of age or over are hypertensive.[1032] The writer believes that these statistics should be accepted with great caution; they do not exclude arteriolar sclerotic disease, they too frequently depend upon single blood pressure measurements, and the question may be raised whether in any instance they represent a true cross-section of the population. The basic fact, perhaps, is that blood pressure is so labile that it is an unreliable guide to the presence or severity of true hypertensive disease. Perera [1586] believes that the incidence of essential hypertension does not exceed 5 per cent, an estimate so different from previous statistics as to emphasize the need for larger and more reliable studies.

In some instances, the hypertensive process is for unknown reasons accelerated, leading to the rapidly fatal form known as the malignant phase of hypertensive disease. It is possible that new causal factors become operative in this accelerated state, since the malignant phase has been reported (if rarely) in patients with no history of pre-existing hypertension. In most instances essential hypertension is a relatively benign disease, and it is not established to what extent it shortens life.[112, 795] Perera [1586] records one woman, still in reasonably good health, who had definitely established hypertension for more than 41 years, whereas survival for more than 20 years is not uncommon.[195] In its more severe forms, however, it may be incapacitating, and its sequelae appear to be the cause of death in a large proportion of the general population. Again to revert to vital statistics, which are anything but satis-

as elsewhere throughout the body (ch. XIV). By *in vitro* tests with smooth muscle or by perfusion preparations (none of them highly specific) small concentrations of renin and hypertensin can be detected in blood, and it has been shown that for a week or so after the induction of Goldblatt hypertension in the dog the renin concentration is increased in the systemic blood.[608] Ultimately, however, this pressor activity disappears despite the persistence of hypertension, which leads some investigators to believe that, after the hypertensive process is initiated by renin secretion, it becomes independently sustained by a neurogenic or other humoral mechanism.[1543] Renin is present in the renal venous blood in approximately the same amount and with the same frequency in hypertensive and normotensive subjects, but occurs in increased amounts in the renal venous blood of some patients with eclampsia, acute glomerulonephritis, and in circulatory failure.[608, 943, 1198]

Other investigators believe that the normal kidney is the source of a substance that has the ability to prevent hypertension, and that it is the absence, destruction, or neutralization of this substance which results in elevated blood pressure.[874, 875] There is also the possibility that pressor agents, formed by failure of deamination, may be involved.[170, 174] Selection between these divergent views (if any of them contains the answer) is impossible at the present time. It may be emphasized that in benign experimental hypertension the arterioles, particularly of the kidneys, undergo hyperplasia and hypertrophy, presumably because of increased 'work' in the face of elevated pressure, but the endarteritis and arteriolar necrosis which characterize the advanced form of the disease in man do not occur.[791]

VDM AND VEM IN EXPERIMENTAL HYPERTENSION

(For definitions of VDM and VEM see p 788)

Shorr, Zweifach, and their collaborators[1531] have shown that, within 30 min. after partial constriction of the renal artery in the dog, VEM appears in the renal venous blood and a few hours later can be detected in the peripheral blood, where significant concentrations remain during the time when the blood pressure is increasing. However, after the pressure has become stabilized at hy-

inadequate venopressor mechanisms, the hypertensive subject is particularly susceptible to hypotension under circumstances that block sympathetic vasomotor tone or impair the venous return to the heart (spinal anesthesia, the pyrogenic reaction, orthostatic syncope, etc.).[230]

HYPERTENSION OF RENAL ORIGIN

Renin

Until something over a decade ago, the invasion of the renal vascular bed, with its sequelae of glomerular and tubular degeneration, was accepted as merely indicative that the kidneys were not immune to the widespread arteriolar sclerosis which also affects the brain and retinae, the skeletal muscles, the coronary vessels, and the vasculature of other viscera. However, impressed by the frequent association between hypertension and acute or chronic glomerulonephritis, which has been recognized since Bright first described nephritis, investigators had attempted to initiate the hypertensive process by partial nephrectomy, reduction of the renal blood supply, or other measures designed to impair renal function. It remained for Goldblatt, Lynch, Hanzal, and Summerville [792] to establish that the blood pressure of the dog and other animals could be permanently elevated to pathologic levels by partial constriction of the renal artery on one side, the other kidney being removed. This demonstration evoked new interest in the possible role of the kidneys in the genesis of essential hypertension, and has stimulated a larger body of experimental work than any other observation in the last two decades.[249,789,790,791,799,1543,1565]

The most generally accepted interpretation of the Goldblatt experiment is that alterations in the renal circulation, not necessarily ischemic in nature, lead to the secretion of renin, a substance first extracted from kidney tissue by Tiegerstedt and Bergman in 1898. Renin is a proteolytic enzyme which is known to react with plasma alpha-2-globulin (hypertensinogen); in this reaction there is liberated an actively pressor polypeptide, angiotonin, or hypertensin, of small molecular weight. When given in pharmacological doses, renin and angiotonin cause vasoconstriction in the kidney as well

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pertensive levels, the blood becomes 'neutral,' due to the presence of large quantities of VDM.

Examination of kidney tissue from chronically hypertensive animals reveals that the kidney has undergone transformation into an organ that has lost the capacity to inactivate VEM and which, therefore, produces this agent continuously, even under aerobic conditions. Although the initial derangement of the VEM inactivating system might have its explanation in the reduced blood flow which immediately follows the application of the clamp to the renal artery, there is no explanation for the persistence of this derangement during chronic hypertension when the renal blood flow has returned to normal.*

The 'neutral' reaction of the blood of the chronically hypertensive dog is attributed to the presence of large quantities of VDM (which is normally absent), and this agent can be uncovered when the blood is incubated with normal kidney tissue in the presence of oxygen to destroy VEM. Thus, a new equilibrium, with both factors present in large amounts, appears to be established after the blood pressure has stabilized at hypertensive levels. The presence of large amounts of VEM can be explained by the derangement of the renal inactivation system, but why the liver should liberate large quantities of VDM is unexplained.

Adrenalectomy in rats leads to a loss of the capacity of renal tissue to elaborate VEM, even in animals maintained on a high salt intake, this deficiency being prevented by DCA. In adrenal insufficiency the blood vessels of the test animals lose their responsiveness to adrenalin as well as to VEM. An intact adrenal cortical mechanism is apparently necessary for the operation of the VEM mechanism, both in the kidney and on the peripheral vessels.

Shorr and his collaborators emphasize that a causal relationship between the VEM mechanism and the development of renal hypertension cannot be established on the present information. VEM in tested doses has no pressor effect, presumably because it acts

* Complete renal ischemia of 150 to 240 min in the rat leads to deterioration of the VEM elaborating mechanism, as might be expected from renal survival studies Forty to 90 min. of ischemia destroys the inactivating mechanism but leaves the VEM elaborating mechanism intact. However, studies of complet ischemia throw little light on the hypertensive mechanism.

on that part of the vascular bed distal to the arterioles which contribute the major variable component to the peripheral resistance and on which angiotonin and other pressor agents have their action. The meta-arterioles and precapillaries contribute relatively little to the peripheral resistance; they are under the dual influence of systemic and local tissue factors; their primary function concerns the distribution of blood within the capillaries and the capillary pressure. At the present time, a relationship between VEM and essential or renal hypertension is purely speculative. If a relationship does exist, it is probably indirect. In response to reduced capillary circulation and tissue anoxia, persistent hyperreactivity of the meta-arterioles and precapillaries may be induced, which may in turn induce arteriolar constriction by humoral or reflex action. But this postulated sequence has not been proved.

HYPERTENSION AND UROLOGIC DISEASE

With the demonstration of the production of a hypertensive state in experimental animals by the Goldblatt technique, the pendulum of interpretation at first swung far to the left, and numerous writers took the position that all essential hypertension in man has its origin, if not in renal ischemia, at least in renal disease. A review of the evidence on the coexistence of hypertension and urologic disease does not bear out this assumption.[1933] The already high incidence of hypertension is not increased by such disease (nephrolithiasis, hydronephrosis, prostatic hypertrophy, intrarenal pelvis, nephroptosis, perinephritis, congenital aplasia, pyelonephritis), and, conversely, the incidence of urologic disease is no greater among hypertensive than among normotensive subjects. At present, the only way a causal relationship between urologic disease and hypertension can be demonstrated in any particular patient is by 'curing' the hypertension by removing the offending organ. Because of the lability of pathologically elevated blood pressure, rigid criteria must be observed: i.e. pre-existing hypertension of some duration must be clearly demonstrated, the blood pressure must be reduced by the operation to normal levels (140/90 or below), and it must remain at normal levels for one year or longer. Review of the literature on unilateral nephrectomy

criteria have apparently been fulfilled in only 47 out of 242 reported operations. In these 47 instances unilateral renal pathology may have been the cause of hypertension, but the very rarity of success (19 per cent), coupled with the evidence that the bulk of urologic disease does not cause hypertension, still leaves a reasonable doubt that they should be so interpreted.*

directed toward the treatment of hypertension reveals that these

RENAL BLOOD FLOW IN EXPERIMENTAL HYPERTENSION

Dock and Rytand,[526] from *in vivo* perfusion studies, concluded that the renal blood flow is not diminished in rats in which hypertension has been induced by subtotal nephrectomy. Levy, Light, and Blalock,[1232] however, using the venous sound method, found that partial constriction of both renal arteries sufficient to produce Goldblatt hypertension in 10 dogs reduced the renal blood flow from an average of 291 cc. to 172 cc. (−41 per cent). The renal oxygen consumption decreased in a parallel manner (−43 per cent), the oxygen arterial-venous difference remaining essentially unchanged (2.9 and 2.8 cc/100 cc.). A similar conclusion with regard to oxygen consumption was reached by Mason, Evers, and Blalock,[1417] using the explanted kidney technique. In all cases reported by Levy *et al.*, the blood pressure in the renal artery distal to the clamp was decreased below the level existing in the femoral artery, averaging 50 mm. and 38 mm. Hg lower in the right and left renal artery, respectively. The reduction in renal blood flow reported by them is in contradiction to all subsequent studies, the reason for the discrepancy being undetermined.

Friedman, Sugarman, and Selzer[716] found that in acute experiments (30 min. duration) constriction of the aorta in anesthetized (pentobarbital) dogs, to such an extent as to reduce the mean pressure below the constriction by 30 to 40 mm. Hg and to greatly reduce the pulse pressure, had no consistent effect on the diodrast clearance but the filtration rate was reduced by an average of 20

* The advisability of nephrectomy must rest upon conservative and recognized surgical indications, and not upon the hope of reducing blood pressure If bilateral disease is present, and it usually is associated with advanced hypertension, nephrectomy may shorten life by removing an important fraction of total available renal function All such unfavorable cases are perhaps not reported in the literature.

per cent. They conclude that the maintenance of renal blood flow in the face of this reduced pressure implies vascular dilatation in the kidneys. If the pressure was reduced for more than 30 min., the renal blood flow uniformly decreased. After restoration of pressure, the filtration rate returned to the control level but the renal blood flow decreased further (−20 per cent), this ischemia persisting for about an hour. Greater reduction in pressure (by 40 to 60 mm. Hg) decreased both the filtration rate (−16.5 per cent) and renal blood flow (−14.5 per cent). Again, on release of the pressure the filtration rate returned to normal but the renal blood flow again decreased further (−24 per cent). From additional experiments in which the constriction was placed above the left but below the right renal artery, these investigators were led to attribute this ischemia to a humoral agent formed in the kidney during the period of reduced mean pressure and pulse pressure.

In similar but chronic experiments on uninephrectomized dogs, they found that the renal blood flow was again maintained despite a marked reduction in mean pressure and pulse pressure, even after a period of 14 days when the dogs had developed hypertension. They conclude that reduction in renal artery pressure (both mean and pulse) is followed by renal vasodilatation and, if the decrease in pressure is not too great, there will be no renal ischemia. During the period of reduced renal artery pressure, however, a humoral agent capable of neutralization by a kidney with

[illegible]

is, however, not necessary for its production, and they infer that renal ischemia is neither the initiating nor the maintaining factor in experimental hypertension.

Corcoran and Page [416] similarly examined renal function in uninephrectomized dogs in which hypertension was induced by constriction of the renal artery or cellophane perinephritis of the remaining kidney some months after [illegible]

[illegible]

and diodrast, they found that the induction of hypertension may occur without constant or persistent changes in the clearance of

any of these substances and without significant changes in Tm_D or Tm_O and, therefore, probably in the absence of renal ischemia. Measurements of the total renal blood from the clearances and ex-

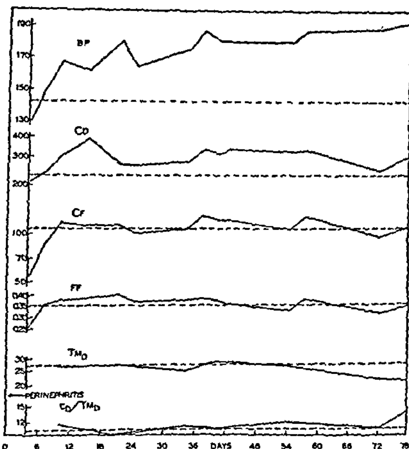


FIGURE 124. *Renal function in a dog with experimental hypertension induced by the application of silk to both kidneys* The dotted lines represent the averages of several control observations on each function made prior to the induction of perinephritis. (Corcoran and Page[414])

traction ratios of phenol red and inulin showed no correlation between mean arterial pressure and renal blood flow, and demonstrated that *hypertension may persist in the absence of renal* ischemia. In one uninephrectomized dog in which hypertension had persisted *for nearly 3 years*, the last observed values were dio-

drast clearance 275, inulin clearance 92 cc., Tm_D 15.4 mg. iodine, and Tm_G 293 mg/sq. m. These values are within the normal range to be expected of a uninephrectomized dog, and were made at a time when retinal hemorrhages and partial retinal detachment boded the onset of the malignant phase. Histological study of the kidney, which weighed 80 gm., showed one small scar of the ischemic type and rare hyalin glomeruli. Data on one dog are given in figure 124, and show that hypertension developed without a decrease in diodrast clearance or the C_D/Tm_D ratio, and without an initial reduction of Tm_D. The late decrease in Tm_D may represent infiltration with scar tissue.

Corcoran and Page note that the rate of renal blood flow in experimental hypertension depends upon a balance between increased arterial pressure and increased renal resistance, the latter arising either from primary arterial compression or compression of the renal parenchyma or, secondarily, to renal vasoconstriction induced by the unopposed activity of the humoral mediators of renal hypertension. The fact that in the hypertensive animal the renal blood flow tends to be maintained at a normal level implies that the increased renal resistance is just about offset by the increase in the mean blood pressure. In the absence of renal ischemia, they conceive the exciting factor leading to the secretion of renin (or other humoral agents) may be a reduction in pulse pressure, or some subtle variation in pulse wave, which follows clamping of the renal artery or development of perinephritic scar tissue. It may be noted that arteriovenous fistula between the renal vessels, leading to renal necrosis, is not accompanied by hypertension.[1213]

Rodbard and Katz [1784] have shown that abscess formation induced by local injections of turpentine or carbon tetrachloride or the subcutaneous implantation of kidney tissue causes a sustained fall in blood pressure in both nephrogenic and spontaneous hypertensive dogs. Stamler, Rodbard, and Katz [1978] find that this reduction in pressure is associated with an increase in renal blood flow. Since the provocative agents are equally effective in eliciting the reduction in blood pressure, it is concluded that the depressor response to the abscess is a non-specific reaction. Abscess production elicits a persistent increase in renal blood flow, but the renal

hyperemia may follow the decrease in blood pressure. The latter is therefore not directly dependent upon relief of renal ischemia. Injury produced by inhalation of chloroform or by oral administration of carbon tetrachloride consistently failed to reduce the blood pressure of hypertensive dogs. Instead, the blood pressure was sometimes elevated. The mechanism involved in the fall in blood pressure, therefore, appears to be part of the pattern of systemic reaction to the abscess. Nephrogenic hypertensive dogs, with and without a reduced renal blood flow, respond to tissue injury with a renal hyperemia as well as do spontaneous hypertensive animals with normal kidneys, indicating that reversible vasoconstriction is involved in the renal ischemia observed in some nephrogenic hypertensive dogs.

Stamler, Katz, and Rodbard [1977] report that, in 6 dogs in which both renal arteries were partially occluded, some showed normal renal function while in others the filtration rate and renal plasma flow were reduced below the normal range, with or without an increase in filtration fraction. Serial observations revealed no tendency for renal function to suffer progressive deterioration, whether the immediate postoperative clearances were normal or reduced and regardless of the duration of hypertension, nor did renal function improve in those animals in which it was immediately depressed postoperatively. In 3 animals that came to autopsy, impaired renal function correlated with gross anatomic alterations in the kidney; whereas the kidney usually showed no pathologic changes when renal function was not depressed,* *normal function did not mean normal anatomy.* The data afford no evidence of the development of collateral circulation in the kidneys of Goldblatt dogs.

Stamler *et al.* have also studied 3 male dogs with spontaneous benign hypertension,† i.e. with persistent pressures in excess of 185/100 mm. Hg of over 2 years' duration. All 3 animals had renal

* In one animal, clearance data within the normal range served only to mask advanced unilateral atrophy accompanied by contralateral compensatory hypertrophy.

† For normal blood pressure in dogs, Katz and his coworkers [1094] analyzed the protocols of 127 trained, unanesthetized dogs and found the mean systolic pressure to be 155 ± 11 mm Hg (range 130 to 185), the mean diastolic pressure 80 ± 6 mm. Hg (range 65 to 100).

clearances within the normal range (PAH clearances of 241, 272, and 294, and filtration rates of 82, 84, and 100 cc. per sq. m.) and on repeated examination renal function remained unchanged for 39, 34, and 64 weeks, respectively. (The last figure is probably equivalent to 7 years, the authors say 10 years, of the human life span.) Pathological studies on 2 of these dogs revealed slight to moderate chronic focal renal lesions and bilateral adrenal cortical adenomatous hyperplasia. The authors suggest that both lesions may be without pathogenic significance. Though these blood pressures may represent the upper range of normal values, they are as truly hypertensive as Goldblatt animals with similar blood pressure elevations Spontaneous canine hypertension may be extrarenal in origin, but whether or not it is related to abnormal adrenal function cannot be determined from the available data.

Stamler *et al* reaffirm that neither dogs with spontaneous benign hypertension nor dogs with chronic nephrogenic hypertension develop the sclerotic changes in the renal, coronary, or cerebral arterioles characteristically complicating long-standing essential hypertension in man, a fact which they believe reflects a species dif- ference in susceptibility to arteriosclerosis rather than a funda- mental difference in the underlying hemodynamic processes. The believe that mechanisms other than elevated blood pressure *per* operate to produce these sclerotic changes.

Stamler, Fishman, Katz, and Rodbard [1975] find that in u anesthetized, spontaneous, and Goldblatt hypertensive dogs, d ing the depressor response to abscess, the cardiac output and bl volume remain normal. The sustained fall in blood pressure is tributable to decreased peripheral resistance. Renal hyper and increased renal fraction are components of the systemi sponse to abscess and indicate a decrease in renal resistance gr than the overall decrease in peripheral resistance.

By contrast, anesthetized (nembutal) hypertensive dogs e increased cardiac output, renal ischemia, and markedly re renal fraction during the depressor response to inflamn These results are interpreted as representing the response combined acute depressor effects of the abscess and of ne anesthesia, the drug inducing a further decrease in total pe resistance. The observed hemodynamic pattern is appa

compensatory response serving to maintain blood pressure. The authors conclude that the cardiodynamic pattern of spontaneous hypertension in dogs is similar to that of Goldblatt and human essential hypertension.

A high protein diet increases the renal plasma flow and filtration rate in dogs with experimental hypertension in a manner which is indistinguishable from the normal animal, another fact which argues against renal ischemia as the primary factor in the genesis of this type of hypertension.[42]

RENAL FUNCTION IN ESSENTIAL HYPERTENSION

Numerous clearance studies are now available on renal function in subjects in all stages of hypertensive disease. The interpretation of all such clearance studies is contingent upon the validity of the clearance method in the diseased kidney. Bradley, Curry, and Bradley,[239] from observations on 14 subjects with well-established hypertensive disease, conclude that a PAH extraction ratio of 0.88 or more may be expected except in very advanced stages of renal injury (C_{PAH} less than 440 cc.), when it may decrease to 0 60. Reubi and Schroeder [1699] report E_{PAH} in 8 patients; all except 3 (0.698, 0.797, and 0.807) were above 0.88. Cargill [328] reports E_{PAH} in 3 patients of 0.87, 0.90, and 0.90. Cargill's data indicate that E_{PAH} is not substantially reduced until the PAH clearance falls below 300 cc., when it may decrease to 0.58. Throughout the following discussion it will be assumed that the diodrast or PAH *clearance, so long as it is above 300 cc., may be taken as a* reliable indication of renal plasma flow.

Investigators are generally agreed that, in many subjects with well-established hypertension, *the renal blood flow is within the* normal statistical range.* In the larger proportion, however, the renal blood flow suffers reduction, the degree of this reduction being interpretable only in relation to the quantity of residual functional tissue. Perhaps the most distinctive change effected in the kidneys by *essential hypertension is the progressive destruction* of tubular tissue, a destruction which can be discovered only by measurements made during tubular saturation. Goldring,

* This may be true only in younger people, but the writer does not believe that the data permit the establishment of any firm correlation with age.

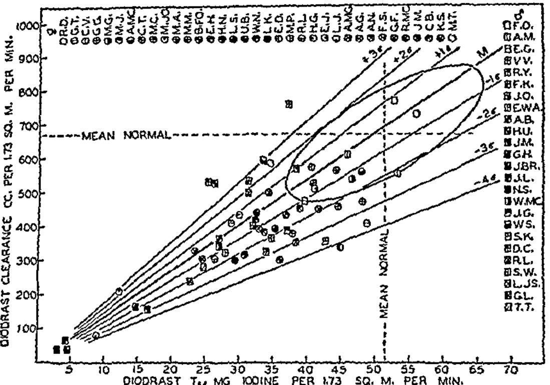


Figure 125. Diodrast clearance in hypertensive subjects related to Tm_D. The statistical background is based on data from normal subjects,[787] the ellipse being calculated to contain 70 per cent of the normal data, and actually containing 72 per cent. (Goldring, Chasis, Ranges, and Smith [788])

INULIN CLEARANCE CC. PER 1.73 SQ. M. PER MIN.

160 140 120 100 80 60 40 20

MEAN NORMAL

+5σ +4σ +3σ +2σ +1σ M −1σ −2σ

5 10 15 20 25 30 35 40 45 50 55 60 65 70

DIODRAST T_M MG IODINE PER 1.73 SQ. M. PER MIN.

FIGURE 126. Inulin clearance in hypertensive subjects related to Tm_D. Statistical background as in figure 125. The ellipse, calculated to contain 70 per cent of the normal data, actually contains 75 per cent. (Goldring, Chasis, Ranges, and Smith[788])

Chasis, Ranges, and Smith[198] therefore analyzed their data on 60 hypertensive subjects in terms of Tm_D.

Figure 125 shows the diodrast clearance (C_D) in relation to Tm_D, plotted against the normal parameters * previously established by these investigators.[197] In their normal subjects the ratio C_D/Tm_D had a mean value of 13.4 ± 1.4 and is here represented by the heavy line, M, the light lines above and below M denoting multiples of the standard deviation (The ellipse was calculated to contain 70 per cent of the normal observations and actually contained 72 per cent.)

If we were to start with a normal (statistical mean) kidney in which $C_D/Tm_D = 13.4$ and were to reduce the quantity of tubular excretory tissue and the renal blood flow by proportional amounts, we should pass down the line M until we reached the intersection of the zero ordinates This is not to imply that the statistical regression line relating C_D to Tm_D in normal subjects extrapolates to zero, for it does not, the concept of proportional regression is merely an artifice convenient to functional interpretation. A variation of the ratio within the limits of $\pm 2\sigma$ would be expected to contain 95 per cent of the normal observations, and it is in keeping with the artifice of proportional regression to conceive that any distribution of the data disproportionate with this statistical expectation is indicative of significant functional changes in C_D, Tm_D, or both.

It will be observed that, with the exception of 3 subjects (F. O., R. D., and G T.), Tm_D is below the mean normal value (51.6 mg. of iodine) and ranges from slightly subnormal to very low values. The lowest values of Tm_D are found in subjects with advanced retinopathy and significant proteinuria. It is evident that in many hypertensive subjects the renal tubules, as judged by Tm_D, have been severely injured, and it may be assumed that this injury proceeds, however irregularly, throughout the course of the disease. It is possible that some tubular injury had occurred in the 3 sub-

* The normal parameters used in these figures are calculated from the limited series of observations reported by Goldring *et al* in 1940, but these data are in good agreement with the larger series published subsequently[198L,1939] and with the data summarized in table XII

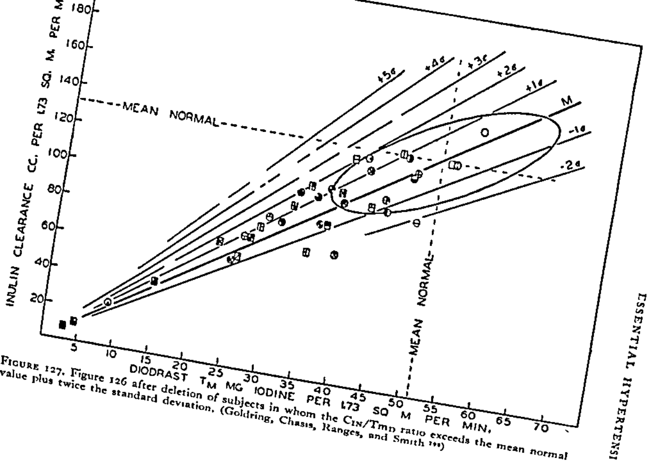


FIGURE 127. Figure 126 after deletion of subjects in whom the C_{IN}/Tm_D ratio exceeds the mean normal value plus twice the standard deviation. (Goldring, Chasis, Ranges, and Smith [199])

jects in whom Tm_D exceeded the mean normal figure, as well as in those in whom Tm_D was above 40 mg. of iodine.

With the exception of 3 subjects (F. O , R. D., and V. V.), C_D is also below the mean normal value (669 cc.) and ranges from slightly subnormal to very low values.

The ratio C_D/Tm_D is distributed about the mean value in an uneven manner, 45 out of 60 subjects falling on or below M. This preponderant distribution below M suggests that some factor is operating in hypertensive subjects to produce a relative ischemia the residual functional tissue.

Figure 126 presents the inulin clearance (C_{IN}) in relation to Tm_D. (Again the ellipse was calculated to contain 70 per cent of the normal observations and actually contained 75 per cent.) In all but 5 subjects (R D , M. C., R. L , F. S., and K. S) C_{IN} is on or below the mean normal value (131 cc.). There is, however, a ndency for C_{IN} to remain within the lower range of normal alues (92 to 131 cc) until Tm_D has been markedly reduced, as shown by the horizontal, leftward displacement of the data.

In spite of the absolute reduction in C_{IN}, its relative value per unit of functional tubular tissue (C_{IN}/Tm_D) exceeds the mean normal value, M, in 43 out of 60 subjects, and in 21 of these it falls above M $+2\sigma$. Three factors might operate to maintain a relatively high filtration rate: (a) increased mean arterial pressure; (b) dilatation of the afferent glomerular arterioles; and (c) the formation of impotent nephrons. We cannot immediately distinguish among these alternative possibilities, but failure to do so is not critically important, since the net result upon the blood flow to the residual functional tissue will be the same, namely, the production of apparent hyperemia in this tissue. In the expectation, therefore, that an abnormally high value of C_{IN}/Tm_D may be expected to be accompanied by an abnormally high value of C_D/Tm_D, a further analysis of the blood flow picture presented in figure 126 may be made as follows: all those subjects, 21 in number, in whom C_{IN}/Tm_D exceed M $+2\sigma$ were deleted, the picture after this deletion is effected being given in figure 127. The remaining subjects are now approximately equally distributed abov and below M, because those in whom the C_{IN}/Tm_D ratio was hi have been deleted.

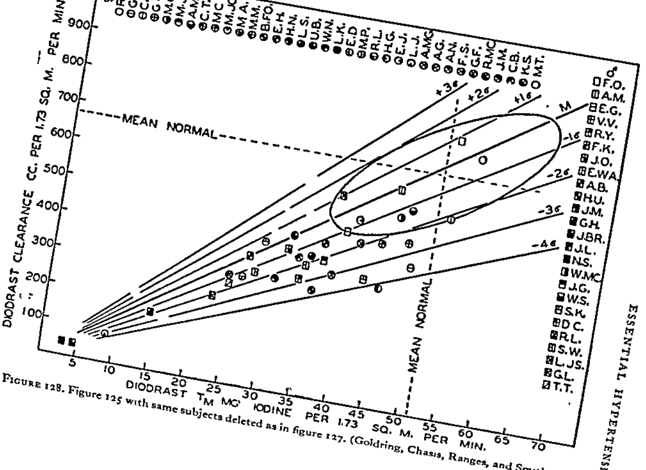


FIGURE 128. Figure 125 with same subjects deleted as in figure 127. (Goldring, Chasis, Ranges, and Smith

Figure 128 is figure 125 with the same subjects deleted, and it will be seen that in the remaining subjects the ratio C_D/Tm_D is in general below, and in some instances far below, the mean normal

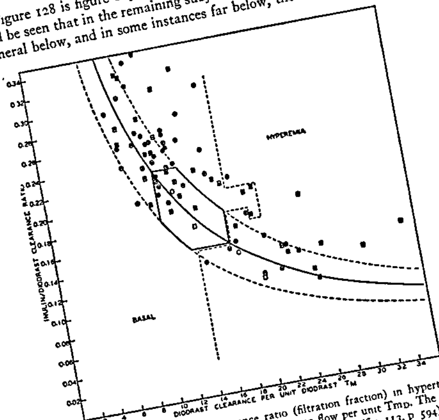


FIGURE 129 Inulin/diodrast clearance ratio (filtration fraction) in hypertensive subjects, related to the effective renal plasma flow per unit Tm_D. The statistical background is taken from data on normal subjects (fig 113, p 594) the hexagon containing 95 per cent of the normal basal data Basal observations on hypertensive subjects are shown to the left of the vertical dotted line, observations during pyrexial hyperemia to the right (Goldring, Chasis, Ranges, and Smith [798])

value. Thus, when those subjects who show a high filtration rate per unit of functional tubular tissue (C_{IN}/Tm_D), presumably because of elevated glomerular pressure and/or the formation of impotent tubules, and in whom we may expect active or vicarious hyperemia to occur in consequence of these circumstances, are

deleted from the picture, it is revealed that in the remaining subjects the renal blood flow per unit of functional tubular tissue is, with 3 exceptions, below the mean normal value, and in many it falls to very low values. This analysis led the authors to conclude

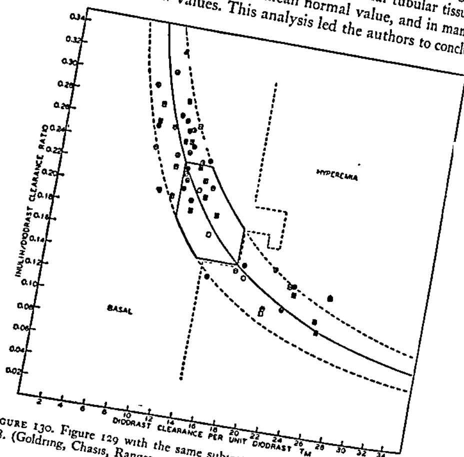


FIGURE 130. Figure 129 with the same subjects deleted as in figures 127 and 128. (Goldring, Chasis, Ranges, and Smith [118])

that some factor is operative in these subjects which tends to produce a relative ischemia of the residual functional tissue. (This ischemic factor may, of course, be operative in the subjects who were deleted because they showed a high C_{IN}/Tm_D ratio, but offset by such factors as were enumerated in defining that group.) Since all these subjects have an elevated mean blood pressure, the cause of this relative ischemia must be an increase in renal resistance.

FILTRATION FRACTION

In normal subjects, the filtration rate tends to remain constant when the renal blood flow is increased during pyrogenic hyperemia or decreased by adrenalin. Under this circumstance, the filtration fraction must vary inversely as C_D, i.e. filtration fraction, when plotted against C_D/Tm_D, will describe a rectangular hyperbola, as shown in figure 115 (ch. XVIII). This rectangular hyperbola, based upon the average normal filtration fraction of 0.19, is reproduced in figures 129 and 130 as a background for the interpretation of the data on hypertensive subjects. These data are divided into two categories: those to the left of the vertical dotted line represent basal observations, and those to the right represent observations made during pyrogenic hyperemia. (The data on pyrogenic hyperemia are discussed below.)

The basal data on the unselected hypertensive series as a whole (fig. 129) show a wide scattering of filtration fraction relative to C_D, though in almost all instances the filtration fraction is greater than the mean normal value of 0.19 and may reach values as high as those reached under the maximal action of adrenalin in normal subjects. In many instances the filtration fraction is excessively high relative to the behavior of the normal kidney during the action of adrenalin, etc. Such a result is to be expected if, as suggested above, there exist in some hypertensive subjects impotent nephrons which supply glomerular filtrate but do not clear the postglomerular blood of diodrast, or if the filtration rate in some nephrons is increased by elevated glomerular pressure. Deletion of the same subjects as before from figure 126 (referring to the basal data only) now shows basal values (fig. 130) of the filtration fraction which, though elevated above the mean normal value, nonetheless fall within the normal parameters with respect to C_D/Tm_D. Thus the selected group again presents a picture of marked renal ischemia induced by moderate to severe arteriolar constriction which is hemodynamically similar to that observed in relation to spontaneous variations in renal blood flow and the action of adrenalin (ch. XVIII).

The hemodynamic nature of the arteriolar changes in hypertensive disease are discussed in chapter XVIII.

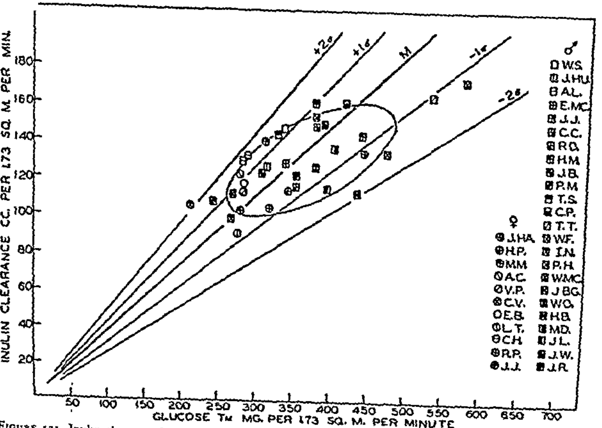


Figure 131 Inulin clearance in normal subjects related to Tmg. The statistical background is the mean (M) normal value of the ratio C_{IN}/Tm_G ± multiples of the standard deviation. The ellipse is calculated from normal data to contain 70 per cent of the observations and actually contains 71 per cent. (Smith, Goldring, Chasis, Ranges, and Bradley [100])

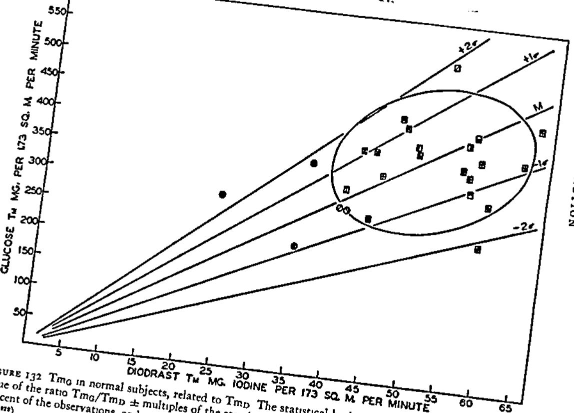


FIGURE 132 Tm_G in normal subjects, related to Tm_D The statistical background is the mean (M) normal value of the ratio Tm_G/Tm_D ± multiples of the standard deviation. The ellipse is calculated to contain 70 per cent of the observations, and actually contains 72 per cent. (Smith, Goldring, Chasis, Ranges, and Bradley [1149])

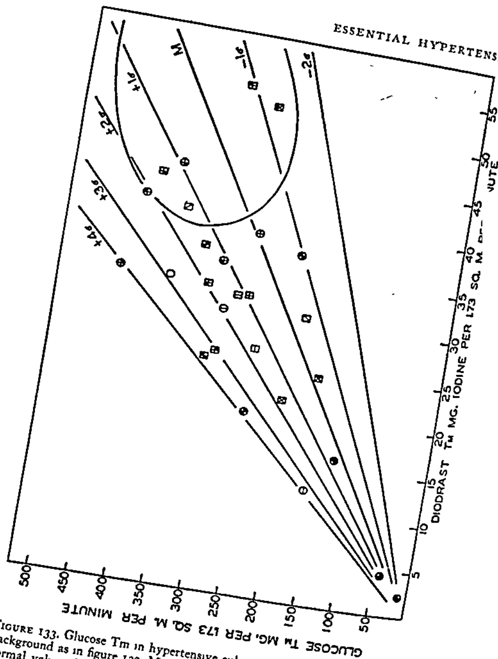


FIGURE 133. Glucose Tm in hypertensive subjects, related to TmD. Statistical background as in figure 132. Most of the observations are low in respect to the normal value of TmD, but normal in respect to TmG. Hence 74 per cent fall above the mean ratio, M, i.e. TmD may be decreased markedly in hypertensive subjects, while TmG remains essentially normal. The term 'impotent' has been

GLUCOSE Tm

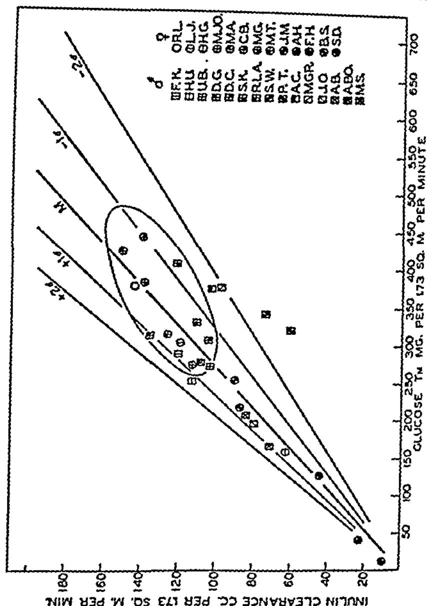
That the reduction of Tm_D in the hypertensive kidney represents in part a loss of specific function rather than tubular obstruction or obliteration is indicated by the tendency for the C_{IN}/Tm_D ratio to rise to supernormal values. This interpretation is supported by the fact that glucose reabsorptive capacity, although ultimately reduced, does not decrease in proportion to Tm_D.[1931, 1939] *The normal relations between the filtration rate and* Tm_G are shown in figure 131, and the relations between Tm_D and Tm_G in figure 132. In hypertensive subjects, the Tm_G/Tm_D ratio increases to supernormal values, as shown in figure 133. The C_{IN}/Tm_G ratio, however, remains narrowly confined to the normal mean value, as shown in figure 134. From this last fact, the authors infer that glucose reabsorption is not specifically impaired in hypertensive disease, and that Tm_G is reduced only when the glomerulus of a nephron is obliterated by vascular changes and the attached tubule is passively cut off from reabsorptive activity. Where, in particular subjects, C_{IN}/Tm_D is above normal, Tm_G/Tm_D is likewise above normal, the increase in both ratios presumably being referable to the appearance of what we have called 'impotent' nephrons.*

In résumé, in hypertensive disease the tubular excretory capacity for diodrast, as measured by Tm_D, is impaired, without an equal impairment in the reabsorptive capacity for glucose, as measured by Tm_G. In the earlier stages of the disease the filtration rate apparently is not affected, though ultimately arteriolar and capillary lesions do impair the filtration bed, and in proportion as this is obliterated Tm_G is reduced below normal values simply because of glomerular destruction. In the terminal stages of the disease, all functions may be reduced to vestigial levels.

* The appropriateness of the term 'impotent' to describe nephrons which have suffered reduction in excretory capacity but not in reabsorptive capacity may be questioned, but the term will continue useful until further data on specific functional attributes are available.

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used to describe tubules which have lost the power of excreting diodrast, but which remain connected to functional glomeruli; the trend depicted here indicates that such 'impotent' tubules can still reabsorb glucose. (Smith, Goldring, Chasis, Ranges, and Bradley [illegible])



... to glucose Tm. ... *Tmc* tend to ... ntained at its ... by the disease *but is decreased only in consequence of reduction of* C_{IN}; *i.e. as glomeruli are deleted from the kidney by arteriolar or glomerular lesions, the attached tubules*

The reduction in Tm_D appears to be the most characteristic impairment of renal function in essential hypertension, and the question arises in regard to the possible significance of this reduction in the etiology of the disease, especially since the evidence on man argues against the primacy of renal ischemia. It is impossible to look upon the tubular excretion of such compounds as diodrast, hippuran, phenol red, etc. as interesting teleologic paradoxes, and it has been suggested [1931,1939] that tubular excretion is a terminal step in a renal metabolic sequence, perhaps involving the conjugation of difficultly catabolizable aromatic residues such as benzoic and phenylacetic acids. Reduction in Tm_D may reflect a deficit in renal metabolic processes anterior to the process of excretion itself. The accumulation of additional evidence on the tubular excretion of normally occurring metabolites (ch. VI) supports the view that this process is highly important in the overall metabolic activities of the body. In this connection, increased interest attaches to the demonstration that Tm_D and Tm_{PAH} in dogs represent functions which are highly sensitive to endocrine activity (ch. XV); at least one process in renal metabolism is demonstrated to be related to factors outside the kidney. It remains to be discovered, however, whether the impairment of renal metabolism which is reflected in a reduction of Tm_D is causally related to the hypertensive process, or whether the impairment is but one of the many degenerative effects of the disease.

BILATERAL RENAL INJURY

Chasis and Redish [358,360] examined unilateral renal function by ureteral catheterization in 21 unselected hypertensive subjects ranging in age from 17 to 57 years. The diodrast clearance and the ratio C_D/Tm_D were nearly the same in the two kidneys of every subject, demonstrating that functional impairment proceeds to an equal degree and at a parallel rate in both kidneys, a circumstance

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necessarily drop out of glucose reabsorption, but glucose reabsorption *per se*

to be expected if renal injury is a result of the hypertensive process but not if renal pathologic disease is primary (fig. 135). The fact that renal injury is bilateral in subjects with hypertensive disease must caution against the unwary removal of one kidney for urologic reasons if a subject has essential hypertension, since unilateral nephrectomy may leave the patient with insufficient function to support life.

THE INDUCTION OF RENAL HYPEREMIA IN HYPERTENSIVE SUBJECTS

The administration of pyrogen to most hypertensive subjects leads to renal hyperemia just as in normal subjects. The degree of hyperemia, as judged by the C_D/Tm_D ratio, appears to be comparable in the two groups. The filtration rate tends to decrease during hyperemia, but so slight is the decrease that it is scarcely significant. (A marked fall in filtration rate in one subject was associated with a severe reaction involving a period of acute peripheral circulatory failure.) Only 2 patients out of 20 failed to show an increase in diodrast clearance exceeding 25 per cent of the basal value; since these subjects had marked retinopathy and proteinuria as well as the lowest values of Tm_D of all the subjects examined with pyrogen, and both died in uremia within a month of the observation, it is inferred that their failure to respond to pyrogen was related to the circumstance that they were in the advanced stage of the disease.

With regard to changes in the filtration fraction during hyperemia, reference may be made to figures 129 and 130, where the hyperemic data are shown to the right of the vertical dotted line. Where the filtration fraction is abnormally high under basal conditions (i.e. lying outside the normal parameters), it retains this anomalous relation during hyperemia, a result consonant with the interpretation that in these subjects the filtration rate is high, relative to Tm_D, because of the existence of impotent tubules or elevated glomerular pressure. Deletion from figure 129 of such subjects leaves a group in which the filtration fraction falls within the normal parameters basally and remains there during hyperemia (fig. 130).

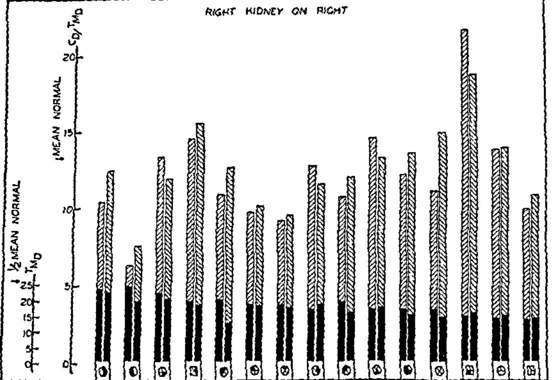


FIGURE 135. A comparison of the diodrast clearance per unit T_{MD} in the separate kidneys of 15 hypertensive subjects. (Chasis and Redish [360])

CHANGES IN DIODRAST Tm DURING HYPEREMIA

Diodrast Tm has special significance in the hyperemic studies, inasmuch as tubules rendered inactive by ischemia under basal conditions might become active, in consequence of opening of vascular channels, during hyperemia. The contribution of a particular tubule to Tm_D will be maximal only so long as the plasma flow to the tubule is adequate at the existing diodrast plasma concentration, P_D, to effect saturation. Consequently, the use of Tm_D to detect inactive (ischemic) tubular tissue is contingent upon P_D in the sense that the higher P_D is, the lower must be the blood flow to the ischemic tubular tissue before the latter will cease to contribute to Tm_D. In terms of the overall function of the two kidneys, the load of diodrast carried to the tubules is the product of the plasma flow times P_D, minus the quantity of diodrast excreted through the glomeruli; if the plasma flow is taken as equal to the diodrast clearance as observed immediately before the measurement of Tm_D, then

$$\text{tubular load} = P_D(C_D - FW\, C_{IN})$$

where FW is the fraction of ultrafiltrable diodrast at the plasma concentration, P_D, actually present during Tm_D determination.

In the observations above, the load/Tm_D ratio was with few exceptions greater during hyperemia than during basal conditions (in part because of the increase in C_D); this circumstance would operate to effect saturation of any tubules which might have been unsaturated in consequence of even severe ischemia during the basal state.

In 3 subjects, Tm_D decreased during hyperemia by more than 10 per cent; in 1 of these there was a distinct decrease in mean blood pressure during Tm_D measurement, which may have reduced perfusion to some parts of the kidney. A second was examined during the accelerated phase of the disease and died within 1 month after the last observation; at necropsy the kidney showed multiple abscesses and necrotizing arteriolar lesions. The observations on the third appeared to be technically satisfactory. In 10 subjects there was no significant change (less than 10 per cent) in Tm_D during hyperemia, despite changes in diodrast clear-

ance ranging up to 88 per cent. In 7 subjects Tm_D increased by more than 10 per cent, the largest increase being 33 per cent, demonstrating that substantial portions of renal parenchyma capable of excreting diodrast were not available to perfusion under basal conditions.

SPONTANEOUS CHANGES IN DIODRAST Tm

It has been noted that diodrast Tm in normal subjects is not significantly changed by the induction of hyperemia or by the administration of adrenalin or caffeine, all of which produce profound disturbances in the renal circulation. In 10 of the hypertensive subjects studied in this series, Tm_D was fairly constant on repeated examination, in some of them over a period of 2 to 3 years. In 2 subjects, however, there were notable but unexplained changes. During 7 weeks when one patient had been continuously in the hospital her Tm_D fell from 53.2 to 41.3 mg. of iodine. This latter value was obtained again after a 3 year period. It is, of course, possible that this represents a rapid progression of renal disease, but this interpretation is rendered less certain by observations on a second patient in whom Tm_D decreased from 41.3 to 29.8 in 13 months, only to rise again to 35.9 during the next 3 years. Even more striking was the increase from 35.9 to 45.1 during hospitalization for 1 month thereafter. Such experiences suggest that in some instances marked fluctuations in Tm_D occur without apparent clinical changes. Whether they are attributable to extreme focal ischemia which excludes some tubules from perfusion, or to intrinsic changes in tubular activity with subsequent regeneration or compensatory hypertrophy in other tubules is undetermined.

The studies above are in agreement with the observations of other investigators. Chesley and Chesley [m2] found that in 11 hypertensive women without history of toxemia of pregnancy, the diodrast clearance ranged from 188 to 557 * cc.; the filtration fraction as estimated from the urea clearance was similarly elevated. The authors note that in hypertensive disease the renal plasma flow may range from normal to low values, while in glomerulone-

* Chesley's normal figures are below those of other investigators, as noted on page 636.

phritis the renal plasma flow may be greatly reduced without hypertension.

Friedman, Selzer, and Rosenblum [712] found in 5 men and 6 women with hypertension of 10 years or more duration that the renal plasma flow averaged 65 and 71 per cent, respectively, of normal. The inulin clearance was reduced to a lesser extent (average 104.3 and 104.6 cc. respectively) and consequently the filtration fraction was elevated (average 0.324 and 0.244 respectively). In 6 subjects with hypertension known to have existed for ½ to 6 years, the reduction in renal plasma flow was equally severe, although the inulin clearance was practically normal. Among 5 subjects whose blood pressure was known to have fallen to normal on recent occasions, and was normal during the test, the renal plasma flow was normal in 2 but reduced in the rest. Friedman and his coworkers point out that there is no correlation between the duration of hypertension and reduction in renal plasma flow or filtration rate. However, when data from 41 persons were classified according to the diastolic blood pressure, it was found that there was a progressive decrease in renal plasma flow and increase in filtration fraction with each 20 mm. Hg increase in pressure, the increase in filtration fraction issuing from the fact that the filtration rate suffered little change. They believe that renal ischemia is probably a local manifestation of generalized systemic vasoconstriction and secondary to the disease.

Steinitz [1999] found in 4 of 6 patients that the renal plasma flow and filtration rate were within the normal range, and he concludes that renal ischemia is not a necessary attribute of essential hypertension. In 3 subjects with malignant hypertension, however, the diodrast clearance ranged from 19.3 to 180 cc., the inulin clearance from 6 to 44 cc.

Foà, Woods, Peet, and Foà [665] studied 20 patients with essential hypertension, whom they divided into two groups. The first group (12 patients) all had a renal blood flow below 549 cc., the average value for all their hypertensive patients. In this group, which may be called clinically severe, the filtration fraction averaged 0.40 and Tm_D 22 mg. of iodine. The blood pressure on admission averaged 239/141 mm. Hg and, after bed rest, 198/120. All except 3 patients had a fixed level of hypertension, or a blood pressure

which fluctuated at high levels and which was scarcely influenced by bed rest. All except 3 had reduced concentrating power, all except 2 showed hemorrhagic retinitis, and in 7 edema of the optic discs was present. In the second group (8 patients) the renal blood flow exceeded 549 cc. The filtration fraction averaged 0.23 and Tm_D 32.9 mg. of iodine. The blood pressure on admission averaged 212/134 and on bed rest 157/95 mm. Hg. All patients in this group had a fluctuating type of blood pressure which dropped on bed rest, and 5 of them had normal concentrating power. The changes in the eye grounds were also less severe. The authors note that markedly reduced renal blood flow correlated well with other signs of advanced disease, whereas no such correlation could be made with the urea clearance, concentrating power, or blood NPN concentration. They found that average ratio of the wall to the lumen of the arterioles in biopsied tissue from the intercostal muscles averaged 1.248 in the first group and 0.9075 in the second, and they suggested that this ratio is roughly indicative of the degree of arteriolar sclerosis.

Findley, Edwards, Clinton, and White [448] report that in 7 out of 12 subjects with uncomplicated hypertension (all were less than 50 years of age; they had normal urea clearances and urinary sediments and showed no eye ground changes or cardiac involvement) Tm_D was in the normal limits, as judged by their own control data. In the remaining 5, Tm_D was reduced below normal. In 6 patients the ratio C_D/Tm_D was normal (13.6) or above, and in 6 this ratio was below normal, sometimes by enough to indicate definite relative ischemia. None of them showed an elevated C_{IN}/Tm_D ratio, indicating that there was no large proportion of impotent tubules. Among 12 subjects with advanced hypertension (3 had chronic glomerulonephritis, 4 had mild congestive failure, 3 were more than 60 years of age, and 2 had uremia and retinal changes), Tm_D was reduced to low normal or subnormal limits in all and the filtration fraction was elevated in all. The authors believed that the evidence was against renal ischemia as a cause of hypertension in a high proportion of subjects.

Friedman and Kasanin [111] report on a pair of identical twins, one of whom had hypertension and coronary disease. In the normotensive twin the renal blood flow was 725 cc., the filtration rate

96 cc., and the filtration fraction 0.24; in the hypertensive twin these figures were 606 and 97.8 cc., and 0.215 (normal male figures, 1166 and 127 cc., 0.19). Why renal function should be so reduced in the normal twin is obscure.

Hilden [1001, 1002] has reported diodrast and urea clearances on 60 patients with hypertensive disease (37 benign, 23 malignant), whom he divides, according to the classification of Keith, Wagener, and Barker,[1103] into 4 groups. A summary of Hilden's data is given in table XVIII.

TABLE XVIII

Urea and Diodrast Clearances in 60 Patients with Hypertensive Disease Studied by Hilden [1001, 1002]

	Per Cent of Normal					
	Urea clearance		Diodrast clearance		Urea/diodrast clearance ratio × 100	
	Mean	Range	Mean	Range	Mean	Range
Group I	84	68–111	78	58–107	13.0	12.4–14.1
Group II	78	45–123	67	34–111	14.4	10.1–18.2
Group III	64	10–117	42	7–88	19.0	13.0–24.9
Group IV	70	26–107	37	13–72	24.0	17.7–29.4

Hilden emphasizes that in the majority of patients in the benign phase (benign cases) the diodrast clearance is normal, arguing against renal ischemia as the cause of this type of hypertension. It will be noted, however, that with progressive disease, as judged by clinical assessment, the diodrast clearance decreases, whereas the urea clearance suffers little reduction, the urea/diodrast clearance ratio rising from 0.13 to 0.24. This fact can be interpreted as issuing from (1) the failure of the filtration rate to decrease *pari passu* with the diodrast clearance because of the formation of impotent nephrons, as noted above, and (2) from the development of hyposthenuria, which, by reducing the degree of concentration of the urine, reduces urea reabsorption. These data emphasize the fact that the urea clearance (even less than the filtration rate) affords no index of the degree of renal injury except in the terminal stages of this disease. If one requires that the filtration rate be reduced to 50 per cent of normal before the rise in blood urea exceeds the variations associated with variations in protein intake

and diuresis, azotemia in the clinical sense may not be reached until Tm_D or Tm_{PAH} has been reduced to 33 per cent or less of normal.

Hamburger and Ryckewaert [893] report mannitol and PAH clearances in 14 subjects with essential hypertension. The mannitol clearance ranged from 47 to 134 cc., and in 8 instances this figure was below 100 cc. The PAH clearance ranged from 104 to 574 cc. and in 11 instances was below 400 cc. The mannitol/PAH clearance ratio ranged from 0.22 to 0.58.

In 32 patients with 'early' essential hypertension, Corcoran, Taylor, and Page [432] report the average filtration rate as 130 ± 22 8 (77 to 192), the diodrast clearance 630 ± 109 (469 to 890), and the renal blood flow 1153 cc (778 to 1662), Tm_D as 47.5 ± 5 5 mg. of iodine (36 to 62). The mean blood pressure was 126 ± 16.2 mm. Hg (98 to 165).

In 76 patients with well-established hypertension the average

154 ± 19 (110 to 200)

In 58 patients with malignant hypertension the average filtration rate was 61 ± 31.7 (15 to 137), the diodrast clearance 216 ± 135 (47 to 564) and the blood flow 369 ± 228 cc. (75 to 1053), Tm_D 21.3 ± 11 mg of iodine (4.5 to 43); mean blood pressure was 176 ± 17.8 mm Hg (134 to 213).

Corcoran, Taylor, and Page note that many (or most) of their patients with 'early' essential hypertension show renal function well within the normal range. The average derived data, C_{IN}/C_D, C_D/Tm_D, and C_{IN}/Tm_D, are equally normal. In the group with established hypertension the mean filtration rate is on the average reduced to 73, the renal plasma flow to 58, the renal blood flow to 65, and Tm_D to 73 per cent of normal, while mean blood pressure has increased to 150 per cent of normal. The derived data are correspondingly abnormal except for a C_{IN}/Tm_D ratio of 99 per cent of normal; the filtration fraction was increased to 127 per cent, and the C_D/Tm_D ratio was reduced to 83 per cent of normal. In the malignant group, the filtration rate is reduced to 48, the renal plasma flow to 32, the blood flow to 34, and Tm_D to 43 per cent of

normal. The filtration fraction remains at 150 per cent of normal, but C_{IN}/Tm_D is 110 per cent, RBF/Tm_D 70 per cent of normal.

In 17 patients with arteriosclerotic (systolic) hypertension, the average filtration rate was 89 ± 29.5 (47 to 124), diodrast clearance 407 ± 101 (220 to 584) and blood flow 710 ± 214 cc. (393 to 1042), Tm_D 35 ± 7.9 mg. of iodine (21 to 51). The mean blood pressure was 134 ± 23 mm. Hg (98 to 180). The pattern in arteriosclerotic hypertension resembles in most respects that seen in their group called established essential hypertension.

Hogeman [1024] reports data on 20 men with essential hypertension: the inulin clearance averaged 91 ± 29.6, the diodrast clearance 262 ± 159, the renal blood flow 523 ± 226 cc., and the filtration fraction 0.343 ± 0.089. In 42 women these figures were 91 ± 21.2, 279 ± 79.3, 495 ± 145, and 0.334 ± 0.066. The data show lower renal function in the average in those patients with retinal changes of grade III to IV, with systolic blood pressure above 210 mm. Hg and diastolic pressure above 120 mm. Hg, and with blood NPN concentration above 40 mg/100 cc., but there was no correlation with the duration of the disease above and below 3 years. Hogeman, with Hilden,[1001] concludes that there is no correlation between diastolic pressure and filtration fraction, contrary to Friedman *et al.*,[114] who include 6 cases of coarctation in their study. Nor is there a correlation between age and filtration fraction or between filtration fraction and filtration rate.

The filtration fraction was elevated (0.185 to 0.281) in the 3 subjects with hypertension and 3 listed as nephrosclerosis reported by Cargill.[328] Only in the last 3 was the renal plasma flow markedly below the normal range.

Attempts have been made to establish a correlation among Tm_D, C_{IN}, and concentrating power in essential hypertension,[417] but clinical experience indicates that such correlations may be fortuitous. Many hypertensive subjects with Tm_D less than 50 per cent of normal show normal concentrating power (specific gravity 1.030). Nor is it possible at this time to categorize the changes in renal function [432] in various types of renal impairment with too great assurance.

RENAL FRACTION

The fraction of the cardiac output that normally goes to the kidneys may be taken as somewhere between 15 and 20 per cent (ch XVII), considerable variability in this renal fraction arising from variations in the cardiac output, which is probably less stable than the renal blood flow. The data of Bolomey, Michie, Michie, Breed, Schreiner, and Lauson [207] show that in the extreme stages of hypertensive disease this fraction may be reduced to 2 per cent or less, reflecting the fact that the cardiac output does not decrease as the renal parenchyma is destroyed, and terminally in a subject with normal cardiac output the scarred and contracted kidneys receive only a small fraction of the blood. It is possible that the obliteration of the renal circulation, which normally contributes one-fifth of the total hemodynamic 'conductance' (reciprocal of resistance) in the circulatory system, exaggerates the rise in mean blood pressure terminally, but this cannot be a significant factor early in the disease when the renal blood is still normal or only slightly reduced.

RENAL OXYGEN CONSUMPTION

Cargill and Hickam [129] find in 11 subjects with hypertension or nephrosclerosis that the oxygen arterial-venous difference falls within the normal range (1.54 ± 0.41 cc/100 cc.). In these subjects, the renal blood flow ranged from 1237 down to 212 cc., which means that the oxygen consumption decreases *pari passu* with the renal blood flow, reflecting in the main the progressive destruction of renal tissue. The residual functional tissue presumably metabolizes at about the normal rate, the defunct tissue is in effect, and for the large part in fact, metabolically nonexistent. They note that in 4 patients with sustained hypertension the renal blood flow and oxygen consumption were normal, demonstrating that in at least some cases the total metabolic activities of the kidney are carried on at the normal level. They believe that oxygen consumption correlates best with filtration rate; accepting this proposed correlation as significant, it might reflect, as they suggest, the lowered metabolic demands of the functionally reduced

kidneys, the filtration rate being a rough estimate of the number of residual nephrons. It would be interesting to know if the oxygen consumption correlated better with Tm_{PAH}, but no data are available.

EFFECTS OF SPINAL ANESTHESIA

Gregory, Levin, Ross, and Bennett[882] studied the effects of spinal anesthesia in 10 hypertensive patients, with anesthesia up to D_3 in all, and with anesthesia up to the clavicle in 2 of them. The inulin clearance fell in every instance in which the blood pressure was lowered (average −32 per cent first hour, −3 per cent secon hour), as did the diodrast clearance (average −38 per cent first hour, −10 per cent second hour). The decrease in clearances roughly paralleled the extent and duration of the fall in blood pressure. In 1 patient, in whom sensory paralysis reached the second interspace and there was complete motor paralysis of the lower extremities, there was no decrease in pressure but a slight rise; in this patient the clearances increased by 18 and 17 per cent. This isolated instance indicates that, if the pressure is maintained, spinal anesthesia may induce some renal vasodilatation, but in general these data argue against any great neurogenic contribution to increased renal vascular resistance, recalling the sit ation in the normal kidney (ch. XIV). However, Gregory an Levin[881] report that in normal and hypertensive subjects durin spinal anesthesia the arterial pressure nearly always decreased before the antecubital venous pressure, and this and other evidence leads them to believe that the hypotension characteristic of spinal anesthesia is a result of interruption of widespread vasomotor function, rather than a decrease in cardiac output.

Corcoran, Taylor, and Page,[431] on the other hand, report that, in most instances, spinal anesthesia is followed by an increase (average 22 per cent) in renal blood flow in patients with hypertension, the filtration rate generally decreasing (average 12 per cent). During caudal anesthesia, the renal blood flow increased by an average of 13 per cent and the filtration rate decreased by an average of 25 per cent. They explain the discrepancy between their esults and those of Gregory *et al.* on the basis that the latter car-ied anesthesia up to D_2, whereas they went only as high as D_5,

and consequently the reduction in blood pressure was somewhat less

Since the mean blood pressure was invariably reduced to levels ranging from 85 to 125 mm. Hg, Corcoran *et al.* conclude that some renal vasodilatation occurred, and that in hypertension a significant proportion of the increased renal vascular resistance is dependent on nerve impulses which are blocked by anesthesia extending to about D5, or that anesthetic denervation sensitizes the renal vasculature to vasodilator influences. There remains, however, a residual supernormal tonus which they attribute to a humoral factor. (The changes in renal arteriolar resistances in these observations have been recalculated by Gomez' equations in chapter XVIII.) Corcoran, Taylor, and Page conclude that the major systemic hemodynamic change induced by spinal or caudal anesthesia in hypertensive subjects is decreased peripheral resistance, and record their opinion that the observations are entirely inconsistent with the view that essential hypertension is a compensation for increased renal vascular resistance, whether due to arteriolar sclerosis or other causes. They also conclude that, whereas spinal and caudal anesthesia lead to an increase in renal blood flow, lumbodorsal sympathectomy does not (*vide infra*). (The time factor is perhaps significant in this respect, since the data indicate that, apart from the vasoconstriction superimposed by neurogenic and humoral factors, the renal circulation in hypertensive subjects retains in great measure that autonomy which characterizes the normal kidney and restores the renal blood flow in the face of wide changes in arterial pressure. This autonomy may serve to defeat both anesthetic and surgical denervation. By the same argument, the fact that the renal blood flow may remain unchanged during a period of hypotension is not a firm argument in favor of denervation hyperemia. The renal circulation would possibly have responded in the same manner had the renal nerves been intact and the hypotension been brought about by any other means.)

Corcoran *et al* imply, from the fact that caudal anesthesia does not produce widespread flaccid paralysis and yet reduces blood pressure and peripheral resistance, that hypotension in the normal as well as in the hypertensive subject is due largely to removal of

neurogenic vasomotor impulses, contrary to the interpretation of Smith, Rovenstine, Goldring, Chasis, and Ranges.[1940] However, they overlook the study by Rovenstine, Popper, and Bradley,[1743] who found by the balistocardiographic method that the cardiac output did decrease, and that the peripheral resistance was maintained at or above control values in 4 normal subjects with sensory anesthesia up to D5, D4, D3, and C6 respectively. Only in 3 subjects has the peripheral resistance decreased slightly (12, 12, and 27 per cent). Moreover, it seems improper to argue the existence of sympathetic vasomotor tonus in the basal state in the normal subject from observations on hypertensive subjects. The trend is toward the acceptance of an important neurogenic contribution to the elevation of blood pressure in the latter. If this argument is applicable to the systemic circulation it may equally well be applicable to the renal vascular bed.

SYMPATHECTOMY

One subject, examined by Goldring *et al.* before and after unilateral lumbodorsal sympathectomy, showed no difference in diodrast clearance or filtration rate between the operated and unoperated side, either basally or during pyrogenic hyperemia. Five subjects reported by Goldring and Chasis [798] examined by ureteral catheterization showed about the same renal plasma flow in both kidneys, and this function did not change significantly after unilateral or bilateral sympathectomy (ch. XIV).

Castleman and Smithwick [334] removed renal biopsies from 100 hypertensive patients in the course of splanchnic resections for hypertension and divided them according to the degree of vascular disease into 5 grades, the proportion falling in each grade being as follows: grade 0, 7 per cent; grade 1, 21 per cent; grade 2, 25 per cent; grade 3, 33 per cent; grade 4, 14 per cent. The patients averaged 39 years of age and were known to have had hypertension for about 6 years. Sixty per cent had 'normal' renal function, as measured by the phenolsulfonphthalein test, and all showed retinal vascular changes ranging from mere arteriolar narrowing to edema with elevation of the optic discs. In contrast to the almost invariable demonstration of well-developed arteriolar disease in the kidneys of hypertensive patients observed post mortem, 28 per

cent of the biopsies showed no or insignificant vascular disease and an additional 25 per cent showed only mild changes. The authors conclude that the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing the hypertension, and that *in many of these, and probably others, the hypertensive state antedated the renal vascular lesion*, which, once established, probably aggravated the hypertension. They believe that their observations are not in keeping with the concept that renal ischemia due to pre-existing renal vascular disease is the cause of essential hypertension. It is of interest to note that 8 adrenal tumors were found in 7 patients. Six were cortical adenomas and 2 were pheochromocytomas. The latter had not provoked paroxysmal attacks of hypertension.

Talbott, Castleman, Smithwick, Melville, and Pecora[2047] attempted to correlate the renal clearances in 20 of these patients with the degree of arteriolar involvement classified by Castleman and Smithwick. Among 9 patients in whom Tm_D was determined, classification and Tm_D were not closely correlated, values of Tm_D of 37 to 67

o, I, II, or II

The ratio C

tive of relative ischemia The average inulin clearance was not *markedly reduced in grades o, I, II, and III (94, 104, 91, 89 cc. respectively)* but it averaged 64 cc. in grade IV. The diodrast clearance showed a progressive decrease: o, 625; I, 552; II, 470; III, 439; IV, 283 cc The filtration fraction was normal in 7 out of 8 cases in grade o, I, and II, and increased in 6 of 11 cases in groups III and IV The average filtration fraction increased progressively with the severity of arteriolar lesions: o, 0.155; I, 0.190; II, 0.193; III, 0.204; IV, 0 233 *The authors conclude that in a fairly high percentage of patients the renal vascular lesions are inadequate to explain the hypertension.* This conclusion has been criticized on the grounds that a small biopsy sample *is inadequate to reveal the status of the renal vascular tree as a whole,* but the conclusion that *hypertension may develop in persons whose renal vascular lesions are no greater than is found in normotensive controls* has been affirmed by *Bell*[115] on broader pathological grounds, and sup-

ported by subsequent observations on the same patients by Castleman and Smithwick.[315]

Bilateral lumbodorsal splanchnicectomy reduced the filtration rate by about 20 per cent in the immediate postoperative period (within 2 weeks), but in 4 to 13 months this had returned to preoperative values. The diodrast clearance did not show any significant change in the immediate postoperative period, but did decrease about 17 per cent within a year and remained approximately the same for the next few years. Nor was there any lasting effect on the filtration fraction. The authors conclude that splanchnicectomy has no effect on the renal circulation.

Corcoran and Page [415] report pre- and postoperative data on renal plasma flow and filtration rate in 2 patients receiving bilateral lumbodorsal sympathectomy. The renal plasma flow was decreased in both, the filtration rate in one, after the operation.

Findley, Clinton, and Edwards [661] report that subdiaphragmatic sympathectomy had little effect on renal function in 5 patients. The diodrast and inulin clearances remained practically unchanged. In 1 patient the ratio C_D/Tm_D increased from 10.5 to 16.5, but this was associated with a decrease in Tm_D over a period of 6 months. They express the view that the changes in blood pressure which occasionally follow surgical intervention are nonspecific in nature and not fundamentally related to the cause of the disease.

Foà, Woods, Peet, and Foà [666] report that bilateral supradiaphragmatic splanchnicectomy with lower dorsal sympathectomy failed to increase the renal blood flow in 17 patients. The fact that the renal blood flow remained relatively constant despite reduction of blood pressure in 8 patients implies that renal vascular resistance was decreased, but not necessarily because of denervation. They believe that the patients with the greatest renal blood flow, the greatest vasomotility, and the least thickening of the systemic arterioles as measured in biopsied material, received the most benefit from the operation.

Southworth [1567] reports that, among 26 patients receiving lumbodorsal splanchnicectomy, renal function was reduced immediately after operation, but after a year or more it returned to the preoperative level. The operation had no lasting effect on the thio-

sulphate/PAH clearance ratio. In 1 patient, however, who apparently had malignant hypertension, marked, real, and sustained improvement in renal function was observed in the 2 years after operation.

Adams, Alving, Sandiford, Grimson, and Scott[6] report that only 1 out of 6 patients showed a decrease in filtration fraction and increase in renal plasma flow after bilateral paravertebral sympathectomy; in all the others the renal plasma flow decreased or remained unchanged.*

Hilden[1004] reports the urea and diodrast clearances in 19 patients 10 days postoperatively, and 10 patients 12 to 18 months after sympathectomy. Ten days after operation the urea clearance was on the whole unchanged, the diodrast clearance slightly increased. Twelve to 18 months after operation both clearances had decreased to a possibly significant extent. He rejects renal ischemia as a primary factor in pathogenesis, and notes that changes in renal function are not related to the clinical results of surgical intervention.

The effects of sympathectomy in reducing blood pressure cannot be explained in terms of direct hemodynamic effects, and indirect physical and chemical mechanisms are apparently involved[2215]

The adrenergic-blocking drug, dihydroergocornine, reduces the renal plasma flow and, to a lesser extent, the filtration rate in both normotensive and hypertensive subjects, the effects indicating renal vasoconstriction. No difference between the two groups could be discerned.[434]

UNILATERAL SYMPATHECTOMY AND ADRENALIN

Chasis and Michie[798] studied the action of adrenalin (0.5 mg. subcutaneous and 0.5 mg. intramuscular) in 5 hypertensive pa-

* Landowne and Alving[1306] have calculated the 'crude' renal resistance as $\frac{\text{blood pressure}}{\text{renal blood flow}} \times 100$ and attempted to correlate this figure with the results of sympathectomy, as reported by several authors They believe that low postoperative diastolic pressures can be significantly related to a 'crude' resistance of less than 22 units This amounts to saying, however, that good operative results can be expected if the blood pressure is relatively low and the renal blood flow high

tients who had received sympathectomy on one side (see table VIII, p. 426). The relative decrease in per cent in renal plasma flow in the sympathectomized/control kidney was 32/27.9, 39.7/41.2, 21.7/19.7, 21.6/25.1, 69.6/68.4. The authors conclude that sympathectomy does not enhance the sensitivity of the renal blood vessels to adrenalin.

UNILATERAL NEPHRECTOMY

Friedman, Selzer, Kreutzmann, and Sampson [712] report that the diodrast clearance was reduced in 4 out of 5 patients having unilateral renal disease and hypertension. It was reduced more in the affected kidney than in the normal one. From the bladder clearances before and after uninephrectomy in 2 cases, and from unilateral studies before nephrectomy in 3, they infer that removal of the diseased kidney was followed by an increase in the renal blood flow and filtration rate of the remaining kidney in all 5 patients. A significant reduction of blood pressure following operation occurred in 3 of the 5 patients, but in none did the blood pressure return to normal despite the fact that in 3 of these patients there was no ischemia of the remaining kidney. They reaffirm the conclusion that renal ischemia may be a concomitant, but is not necessarily a causative factor in the pathogenesis of essential hypertension.

Weiss and Chasis [2159] examined a hypertensive patient in whom there was an atrophic pyelonephritic left kidney. The right kidney preoperatively showed a filtration rate of 84 cc. and a diodrast clearance of 386 cc.; Tm_D was 45.4 mg. of iodine and C_D/Tm_D 8.5. Except for a moderate deficit in the first figure, this single kidney had almost the function of 2 normal kidneys. The left kidney showed a filtration rate of 17 and a diodrast clearance of 55.7 cc., Tm_D of 3.0 mg. of iodine, and C_D/Tm_D of 18.4, showing advanced atrophic changes. Two and one-half months postoperatively, the filtration rate on the right side had increased to 95.8 cc. and the diodrast clearance to 593 cc., Tm_D to 48.4, and C_D/Tm_D to 12.2, showing some stimulation from uninephrectomy. The right kidney was now fully equal to 2 normal kidneys. The blood pressure was not affected by uninephrectomy, and the authors conclude that in

this patient unilateral renal disease was not causally related to hypertension.

NEPHROPTOSIS

McCann and Romansky[1316] report functional studies on 5 subjects with essential hypertension with nephroptosis. The renal plasma flow was consistently lower when measured in the erect position as compared with the value obtained after a period of recumbency of 2 to 5 days. The filtration rate changed little, but in each case the filtration fraction increased. Five normal subjects and 2 with hypertension but without nephroptosis showed negligible changes in renal plasma flow in the erect position. It appears that the movement of one or both kidneys sufficed to reduce the renal circulation, but whether this circumstance is related to the existence of hypertension must remain an open question.

PREGNANCY

During pregnancy, the renal blood flow appears, if anything, to be slightly increased, as indicated by the C_D/Tm_D ratio in women with essential hypertension uncomplicated by specific toxemia. The filtration rate and Tm_D are unaffected.[2162]

DIET

Chasis, Goldring, Breed, Schreiner, and Bolomey[355] examined 10 hypertensive patients while maintained on a ward diet, and subsequently on the low-salt rice diet recommended by Kempner.[1103] The rice diet led to a decrease in filtration rate, renal plasma flow, and Tm_{PAH} in most instances. The filtration rate and renal plasma flow returned to or toward the control level on addition of salt to the rice diet, but Tm_{PAH} underwent a further decrease in 4 out of 5 patients who took salt. When the ward diet was reinstituted in 3 patients in whom Tm_{PAH} had been depressed in the rice diet, this function returned to the control value in 2 and approximated it in 1. The authors interpret the reduction of Tm_{PAH} on the rice diet as a deleterious but apparently reversible effect. Similar results have been recorded in a preliminary note by Weston, Hellman, Escher, and Leiter[2160]

CHLORIDE CLEARANCE

Farnsworth and Barker [618, 619, 620] report that in normal subjects the U/P ratio of chloride correlates positively with the U/P ratio of inulin, the regression line extrapolating to zero. This means that, in any one subject, the chloride/inulin clearance ratio is unaffected by the urine volume, as would be anticipated if chloride reabsorption were itself independent of urine volume, and that active reabsorption will reduce the chloride U/P ratio below 1.0 as diuresis reduces the inulin U/P ratio below some value (usually about 60) which is itself determined by the clearance ratio. In hypertensives, the chloride clearance seems to be susceptible to urine flow but the data do not permit a firm conclusion on this point. The data as recorded show a chloride/inulin clearance ratio some 3 times greater in hypertensives (0.055) than in normal subjects (0.0189) on a regular ward diet, but the figures are suspect: the average chloride clearance in the normal subjects is 1.84 cc/min.; assuming filtrable chloride to be 103 mEq/liter, this would mean the excretion of 15.8 gm/day of salt, while the average chloride clearance in the hypertensive subjects of 4.3 cc. would mean the excretion of 36 gm/day of salt. It seems probable that chloride excretion in both groups was promoted by the use of saline in the clearance test, and hence the difference between the two groups is difficult to interpret. Since hypertensive subjects can keep themselves in salt balance on as low an intake as normal subjects, it is clear that they suffer no excessive loss of chloride.

MALIGNANT NEPHROSCLEROSIS

Between 5 and 10 per cent of patients who die of hypertensive disease die of so-called malignant nephrosclerosis. This condition consists of a fulminating necrotizing renal arteriolitis and appears almost always to be preceded by a shorter or longer period of benign hypertension. Opinion is divided on the true relationship between the two diseases, and malignant nephrosclerosis bears a close resemblance to periarteritis nodosa. It is characterized by weight loss, severe hypertension, marked eye-ground changes, and rapid decay of renal function.

Chesley [311] has reported clearance observations on 3 women in

whom malignant nephrosclerosis occurred contemporarily with, but not necessarily with any causal relation to, pregnancy. In 1 of these patients, when first examined, the renal blood flow was 119 per cent, the filtration rate 141 per cent, the urea clearance 118 per cent, and the uric acid clearance 133 per cent of normal. Rapid deterioration of renal function occurred and within 90 days renal blood flow and Tm_{PAH} were reduced to below 20 per cent of normal. The urea clearance continued its downward course and death in uremia occurred after about 7 months. These data, and data on the urea clearance in the other 2 patients, indicate that in this disease renal function may deteriorate from essentially normal levels to uremic abyss within a period of a few weeks or months.

A patient studied by Brod,[260] in what was apparently the terminal stage of malignant nephrosclerosis associated with chronic pyelonephritis, showed evidence of back diffusion of endogenous creatinine chromogen and of PAH.

HUMORAL FACTORS IN RENAL ISCHEMIA

In view of the fact that the arteriolar lesions in the hypertensive kidney are most evident in the preglomerular and afferent arterioles, and that these lesions are, in extreme instances, of such a nature as to narrow the lumen, it would seem plausible to attribute renal ischemia and the progressive impairment of the renal parenchyma to these arteriolar lesions. This interpretation is undoubtedly in part correct but it must be cautiously qualified. It can be accepted that arteriolar sclerosis will contribute to the reduction in filtration rate, renal blood flow, and Tm_D by the forthright ischemic obliteration of glomerular and tubular tissue without excluding other factors. It has been noted above that reduction [illegible]

many subjects with only moderate renal injury, as shown in figures 125 and 126. The only interpretation that can be given to this fact is that tubular excretory function (as judged by Tm_D, at least) is impaired independently of such arteriolar lesions as obliterate the glomerular circulation. At this time it seems improbable that this tubular impairment can be attributed to ischemic injury, and we

may continue to seek some other explanation as mysterious as the origin of the arteriolar lesions themselves.

Moreover, at every stage of renal injury, until parenchymal destruction has reached its most advanced stages, there is superimposed upon the residual functional tissue an ischemic process of a vasomotor, reversible nature, as is shown by the fact that as great a relative increase in renal blood flow may be induced by the pyrexial reaction in hypertensive patients as in normal subjects. Pyrexial hyperemia fails only when the renal parenchyma has been reduced to a contracted mass of scar tissue with a few vascular conduits that have lost all vasomotor lability. Conversely, until this late stage, the renal vasculature retains its vasomotor responses to autonomic stimuli which in the normal subject typically call forth renal vasoconstriction. Some of this enhanced vasomotor tonus may have a neurogenic basis, but that this is not the entire explanation is demonstrated by the fact that the various operations intended to denervate the kidneys fail in general to increase the renal blood flow or decrease the filtration fraction. Admitting the difficulty of establishing complete denervation of the human kidney, and recognizing that the evidence above does not exclude a local or myogenic origin for the increased resistance, Goldring *et al.*[791] concluded that one or more vasoconstrictor factors are present in the blood, in at least some instances, and especially those in which the ratio C_D/Tm_D is low. This factor or factors may of course contribute to the enhanced vasomotor tone throughout the body. However, since many pressor amines (adrenalin, neosynephrin, cobefrin, tyramine, paradrinol, etc.) produce a type of renal ischemia which can scarcely be distinguished from that of angiotonin by renal hemodynamics, there is little warrant to believe that the humoral factor in essential hypertension is angiotonin. It has been noted, moreover, that renin is not demonstrable in the renal venous blood of hypertensive subjects, even though it is demonstrable in the venous blood in normotensive subjects under certain conditions of renal ischemia and, in some instances, of chronic congestive heart failure. What pressor substances may be involved in essential hypertension remains to be determined. Goldman, Kriss, Futcher, and Schroeder [793] report that transfusion of arterial blood from hypertensive or normo-

tensive subjects into others with hypertension had no consistent effect in the latter upon the filtration rate, renal plasma flow, or filtration fraction. Hypertensive blood did, however, tend to elevate the diastolic pressure of the recipients to a greater extent than

[illegible]

stances of amine nature in the arterial blood of hypertensive subjects, recalling the significance of oxidative deamination.[170, 174] To show that such agents are causally rather than secondarily related to the disease may, however, prove difficult.

Shorr, Zweifach, and their collaborators[1881, 1883] report that in 12 subjects with essential hypertension the blood contained large amounts of both VEM and VDM, but in such balanced proportions as to give it a neutral character in the test animal. Separation can be effected only by incubating the blood with normal kidney tissue to destroy the VEM, unmasking the VDM. The situation is similar to that in the chronically hypertensive dog, and is no more intelligible at the moment. Since the site of action of VEM is the meta-arteriole rather than the arteriole proper, it is to be anticipated not that it would have a direct pressor action but that its influence would be mediated through the (at present) poorly understood mechanisms mediating among arterial pressure, capillary pressure, extracellular fluid volume, and other related physiological variables

It may be noted that the hepatic blood flow was within the normal limits in 12 hypertensive subjects examined by Culbertson, Wilkins, Ingelfinger, and Bradley.[241, 468]

PATHOGENESIS OF ESSENTIAL HYPERTENSION

In the opinion of most observers, the cause of essential hypertension remains unknown.* The position of those who believe that

* Space does not permit the inclusion here of Volhard's theory of hypertension, which leads him to divide the disease into two types, 'red' and 'pale' hypertension. Volhard's views, which are widely accepted in Europe, are in some respects in agreement with those stated here, in other respects in disagreement. They have recently been well summarized by him in the *Festschrift for Thomas Addis.*[illegible]

the kidney is primarily responsible is well presented by Goldblatt:[791]

'The many similarities between human essential hypertension associated with renal vascular disease and experimental renal hypertension suggest but do not prove that the former may also be of renal origin. Even if the renal origin of this form of hypertension should become established, it would still remain necessary to determine the cause of the arterial and arteriolar sclerosis which, when it affects the kidneys to a sufficient degree, initiates the humoral mechanism of the hypertension. The failure of animals to develop widespread arterial and arteriolar sclerosis, even after years of hypertension without accompanying impairment of renal excretory function (the benign phase), does not lend support to the view that hypertension is a sufficient condition for the production of vascular sclerosis. It must be admitted, however, that this may mean only that the blood vessels of animals are less sensitive than human vessels to the effect of increased intravascular tension alone, although they appear to be even more sensitive to the conditions which determine the necrotizing vascular changes of the malignant phase of hypertension. Because the probable primary significance of renal arterial and arteriolar sclerosis has been indicated by experimental studies, the cause of vascular disease has now become the most important problem in the future investigation of the pathogenesis of hypertension.'

Against the renal interpretation are many facts, some of them cited in preceding pages, no one of them constituting proof of a non-renal origin, but which collectively lead many investigators to reject the renal theory. Smirk,[1912] in a notable review of the large literature on this subject, makes a number of important points:

Certain geographical environments favor higher 'normal' blood pressures, while other environments favor lower 'normal' pressures. Populations exhibiting higher 'normal' pressures have a higher incidence of essential hypertension—whether because of environment or racial predisposition is undetermined. Overweight is associated with a tendency to higher blood pressure and, in the course of time, a higher incidence of essential hypertension. The converse is also true. The tendency to exhibit transient hypertension in response to mental and other stimuli indicates a physiological make-up which is likely to express itself in daily life by ab-

normally strong and frequent blood pressure elevations, which, if sufficiently frequent and prolonged, predispose toward the development of essential hypertension. Distinction should be made between 'basal' pressure (dreamless sleep, narcosis, hypnosis) and 'supplemental' pressure (physical or mental excitation). Most 'casual' blood pressures are somewhere in between.

The evidence indicates that elevation of blood pressure is usually manifest, at least in young people, before characteristic changes appear in the kidney and other organs. Prolonged elevation of pressure leads to medial hypertrophy in the smaller arteries and arterioles and perhaps to increased elastic tissue and intimal hyperplasia, these arteriolar changes being usually most pronounced in the kidneys. Such changes are generally interpreted as being compensatory to increased work (pressure) in the arteriolar tree; they may, however, contribute to a vicious cycle by further increasing peripheral resistance, despite the fact that this increase is primarily active rather than passive With other factors (neurogenic, endocrine, humoral) contributing, a vicious cycle may be established so that supplemental increases in blood pressure may outlast the stimuli which caused them. Smirk believes that malignant hypertension is not simply an accelerated form of benign hypertension but involves some additional factor.

The factors that in various combinations may contribute to essential hypertension include (a) inelasticity of the large arteries, (b) exaggerated contraction of hypertrophied arterioles, (c) release of pressor agents from ischemic kidneys, (d) to a very minor degree increased passive resistance of hypertrophied arterioles, and (e) an unknown non-renal factor or factors capable of perpetuating certain blood pressure increases after the primary exciting causes have ceased to operate.

Though Smirk does not call it such, the foregoing view of the pathogenesis of essential hypertension is essentially a polyphyletic one. The causes and contributory factors may be different in different individuals His view recognizes, with many American investigators, that the renal vasculature is frequently, if not usually, as much the victim of arteriolar sclerosis as is the vasculature of the retinae, heart, skeletal muscles, and viscera.

If it is assumed that hypertensive disease is the result of a multitude of microscopic Goldblatt clamps placed upon the renal arterioles, then it must be recognized that the arteriolar disease, which itself remains unexplained, is the primary event, and there remains no reason to believe that this disease necessarily arises from altered renal metabolism. It has been suggested that renal ischemia or some other disturbance of the renal circulation is brought about by neurogenic constriction of the renal arterioles mediated through the sympathetic nervous system. The proponents of this view create an argument by inference from the facts that the renal circulation is sacrificed in the emergencies of shock, hemorrhage, the circulatory failure of syncope, etc., and that renal vasoconstriction can be initiated by fright, pain, and by an acutely precipitated mental conflict stemming from psychoneurosis. This view implies that the stresses of modern life initiate the hypertensive process along the lines of the Goldblatt experiment by the functional constriction of the renal arterioles. If true, the hypertensive process when once initiated must become independent of the kidneys,[1813] for what must be nearly complete renal denervation effected by sympathectomy does not effect a cure.[885,1951] It may be noted in this connection that in dogs repetitive stimulation of the renal nerves, which produces renal ischemia and elevation of blood pressure during the period of excitation, when applied for 22 out of 24 hr. every day for a month, fails to produce a chronic hypertensive state.[1153]

The writer has elsewhere [1933] suggested that, had someone placed a clamp on the pancreatic artery before the days of Minkowski and obtained diabetes, he might well have been led to the theory that all diabetes is due to pancreatic ischemia or some other disturbance in the pancreatic circulation. This is, of course, not true; it is probably a very rare case of diabetes mellitus in which the pancreatic circulation plays any part; in some instances diabetes possibly can be attributed to a congenital deficiency of islet tissue, in some cases to pituitary dysfunction, and in some cases to a disturbance in the adrenal cortex, and not all investigators are agreed that this enumeration exhausts the list.

Among the factors, not emphasized by Smirk, which have been

indicted as contributing to the genesis of essential hypertension are the adrenal cortex,[1547, 1587, 1590, 1591, 1664, 1831] dietary deficiency in early life,[134] the anterior pituitary and the neurohypophysis, genetic predisposition, psychogenic strain, and personality disorders. Findley [646] has recently brought together numerous lines of evidence that suggest to him that hypertension and many allied disorders of aging are due to hypofunction of the neurohypophysis. He has suggested that diminished secretion by this gland results in degeneration of the basophilic cells of the anterior pituitary and of their respective target organs and leads to increased tissue sensitivity to various pressor hormones.

The psychiatrist has reported from investigation of a few hypertensive individuals that such persons tend to display exaggerated dependent strivings, submissiveness coupled with stubbornness, feelings of weakness and defenselessness, suppression of hostility, fear of injury, and emotional detachment that may lead to acute emotional disorders; that essential hypertension may be a somatic manifestation of a psychoneurotic condition based on excessive and inhibited hostile impulses; that protracted resentment may be a specific *leit motif* running through the anxiety and insecurity of the emotional pattern.[60, 1696, 2158] However, the significance of such psychoneurotic disturbances can scarcely be evaluated in the absence of a comparable assessment of conflict, suppression of hostility, fear of injury, and the like in the large number of people who do not have hypertensive disease.

That there is an important autonomic (and emotional) component in the disease is admitted by all investigators,[638, 860] an emotional component which is more important with respect to symptoms than blood pressure itself. It has long been established that headache, restlessness, sleeplessness, and other subjective symptoms can frequently be relieved not only by sedation but by confident reassurance.[87] The blood pressure falls and becomes stabilized at a lower level in a significant number of patients after repeated measurements are begun by the same person;[1590] blood pressures taken at home by the instructed patient are frequently lower than those taken in the clinic,[89] reduction of pressure, sometimes of a substantial degree, is frequently observed to follow pro-

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longed bed rest or even ambulatory hospitalization; * even when the pressure is taken routinely by a familiar nurse during hospitalization, successive readings at the same sitting may be highly variable and the mean values over a period of weeks may fluctuate markedly. But, as Bradley [230] observes, the emotional component is so variable from person to person and from time to time that it can scarcely be accorded more than an incidental role in pathogenesis, although the autonomic nervous system must at least be accounted a major factor in dictating the pressure level. This lability of blood pressure makes it difficult, except under rigorously controlled circumstances, to obtain a base line from which to judge the effectiveness of any therapy.

Most if not all forms of therapy have allegedly had some success in the alleviation of symptoms, if not in the reduction of blood pressure.[744] The only element they have in common, however, as

* *It is well recognized that in many subjects with essential hypertension the blood pressure will fall on bed rest, and even in consequence of admission to a hospital. Goldring, Head, and Chasis (pers. com.) have examined the records of 91 patients with essential hypertension but without signs of cardiac failure or myocardial infarction, who were admitted to Bellevue Hospital for observation but who received no therapy. They were maintained on the ambulatory ward routine and regular diet. The periods of observation ranged from 5 to 131 days. Six to 9 blood pressure determinations were made daily by the same nurse.*

Of this group, 89 1 per cent showed some fall in systolic pressure, 18.7 per cent showed a reduction of 10 to 25 mm , 25 3 per cent a reduction of 26 to 40 mm., and 45.1 per cent a reduction exceeding 40 mm. Hg. Of this total group, 42 per cent fell below 150 mm. and 48 1 per cent showed a subsequent rise. Only 32 4 per cent of those falling below 150 mm showed a subsequent rise.

A decrease in diastolic pressure was observed in 85.7 per cent; 42.9 per cent showed a reduction of 10 to 25 mm , 28.6 per cent a reduction of 26 to 40 mm., and 14 3 per cent a reduction exceeding 40 mm Of this total group 48.7 per cent fell below 95 mm., and 30 8 per cent showed a subsequent rise. Only 21.1 per cent of those falling below 95 mm showed a subsequent rise For those patients who showed a significant decrease (i.e. a decrease in either systolic or diastolic pressure of 10 mm. or more) the time relationship between the day of onset and the number of days required to reach a minimal pressure was determined by plotting the day of onset against the latter figure In 81 patients whose systolic pressure decreased, 47 or 58.0 per cent reached a minimal value in the first 10 days. In 78 patients whose diastolic pressures decreased, 47 or 60 3 per cent reached a minimal value within the first 10 days. However, individual variations reveal that neither the systolic nor the diastolic pressure may start to decrease until the fiftieth day of hospitalization, and the minimal values may not occur until more than 30 days thereafter.

Ayman[87] long ago noted, is the 'enthusiastic treatment of a worried patient.' The restoration of renal function, like the arrest of the vascular disease itself, is at present an unsolved problem.

Much more must be known about the disease before full assessment can be made of such therapeutic measures as involve restriction of salt intake,[1304] of salt intake and protein,[254,255,1108,1305] or of sympathectomy.[88,1014,1931,1932,2218]

CHAPTER XXIV

Acute Renal Failure Related to Traumatic and Toxic Injuries

Azotemia may be precipitated by any circumstance that interferes with renal function, quite independently of the presence of renal disease or even actual injury of the kidneys. Such circumstances are usually complex. For example, postoperative edema of the ureteral-vesicle junction may obstruct the flow of urine through the urinary papillae, though simultaneous reflex renal ischemia is by no means excluded as a participating factor. Tubular obstruction can result from the precipitation of poorly soluble sulfa drugs in the distal tubule and collecting ducts, and produce oliguria by simple obstruction; yet the renal vasculature may participate in the allergic reaction evoked in some sensitive persons by sulfa drugs and other agents, and precipitation of relatively insoluble materials may occur secondarily to the resulting ischemic oliguria.[4, 652]

In many other circumstances, discussed in chapter XXI, circulatory insufficiency as a primary event may lead to azotemia through reduction in renal function by the production of renal ischemia. Among such precipitating factors are hemorrhage, traumatic shock, cardiac failure, and disturbances which lead to dehydration by loss of salt and water, such as vomiting, hematemesis, diarrhea, burns, diabetic coma, and adrenal insufficiency.[810] In such conditions, the azotemi [illegible] tly designated

as extrarenal or prerenal. This designation is chiefly useful in indicating that renal disease is not *per se* responsible for oliguria and nitrogen retention, and that relief from renal insufficiency may be expected if the extrarenal disturbance is rectified. The assumption of a benign prognosis for prerenal azotemia must, however, be tempered by the realization that prolonged renal ischemia can lead to protracted or irreversible renal injury. The borderline between a benign renal ischemia and one producing irreversible damage is not sharply defined.

In none of the circumstances above is it possible to say to what extent vasoconstriction is mediated via the vasomotor nerves, by systemic humoral agents, or by direct action on the renal arterioles Hence any attempt at the present time to classify mechanisms leading to oliguria and azotemia on a physiological basis would be specious. It is, however, in accord with current concepts to speak of renal insufficiency resulting from the recent imposition of an external noxious stimulus as acute renal failure, the expression serving merely to exclude benign renal ischemia and chronic renal disease.

ACUTE RENAL FAILURE

Acute renal failure may occur in such a variety of circumstances that merely for the sake of brevity it is convenient to list some of them categorically:[403]

Shock: gunshot wounds, head injury, ureteroplacental damage, postpartum hemorrhage, concealed hemorrhage, septic abortion, vascular injury, anoxia, carbon monoxide poisoning, and shock, however caused.

Disturbances in electrolyte balance: hematemesis, pyloric stenosis, excessive vomiting, acidosis, alkalosis, cholera and other diarrheas, Addison's disease, hypochloremia, diabetic coma, intestinal obstruction, pernicious anemia, pneumonia.

Pigment excretion. crush injury, incompatible blood transfusion, burns, yellow fever, blackwater fever, equine paralytic myohemoglobinuria, Weil's disease, heat stroke, icterus neonatorum, non-traumatic muscular ischemia.

Allergy: incompatible blood transfusion, eclampsia, serum sickness, sulfonamide sensitivity, staphylococcal toxin, meningococcus toxin, typhus fever, favism.

Chemicals: uranium, mercury, bismuth, oxalate, tartrate, bichromate, tetrathionate, phosphorus, alloxan, cresol, uric acid and carbon tetrachloride (one of the most common offenders), mushroom and possibly many other organic poisons, and the bite of the Black Widow spider.

This listing is incomplete, imperfect, and wholly without relation to the sequence of physiological events that leads to renal injury. The only factor in common is renal injury, and our present problem is to examine the sequence of physiological events that leads to it.

NEPHROTOXIC AGENTS

Uranium

That the toxic effects of uranium salts are chiefly if not solely attributable to a nephrotoxic action was shown by Leconte in 1854. Uranium induces an initial polyuria followed by oliguria and anuria. Although the glomeruli develop obliterative connective tissue changes of varying degrees of severity, the main point of action is on the distal portion of the proximal tubule.[1354, 1549] MacNider[1354, 1355, 1357, 1358, 1359, 1360, 1361] has shown that intoxication with sub-lethal doses in dogs leads to degenerative changes in the proximal tubule epithelium. The cells swell, the cytoplasm becomes cloudy, and the luminal aspect tends to disintegrate. Regeneration of typical proximal epithelium may occur from such cells as are not too severely injured; such regenerated epithelium has no increased resistance to uranium. Or regeneration may occur as an ingrowth of cells or as syncytial buds from cells in the terminal portion of the proximal tubule; this type of regenerated epithelium is cytologically entirely different from normal tissue in that it is flatter and the brush border, if present, is difficult to demonstrate. These cells are remarkably resistant to a second attempt at uranium intoxication and apparently increase the overall resistance of the animal. Similar atypical flat hepatic cells are formed by regeneration after liver injury by uranium, and a comparable transformation occurs spontaneously in the proximal tubule of senile animals, although uranium is more toxic for old than for young dogs. Intoxication is characterized by severe acidosis,

and some protection is afforded by the administration of sodium carbonate, bicarbonate, or citrate.

Richards, Westfall, and Bott [771] found in one dog poisoned with uranium that the creatinine/inulin clearance ratio ranged from 0.98 down to 0.71 (average 0.87) at urine flows of 0.5 cc/min. or more and at inulin clearances of 50 to 67 cc., indicating back diffusion of creatinine under conditions where there should be little if any loss of inulin from the tubular urine. The mean urea/inulin clearance ratio (14 observations) was also lower (0.35) than normal (0.56) In a second dog, the filtration rate was reduced but there was no evidence of back diffusion as judged by the clearance ratios. In both dogs concentrating power was moderately reduced.

Hayman, Shumway, Dumke, and Miller [345] found that uranium intoxication in dogs caused a marked decrease in the inulin, creatinine, and urea clearances, with concomitant azotemia. The renal blood flow, as calculated from the inulin and creatinine extraction ratios in 2 dogs, was not materially reduced, confirming older evidence on this point which they review. Studies were made during dehydration in order to evaluate concentrating capacity; the urine flow increased from the control range of 51 to 123 cc. to the range of 148 to 663 cc/day after uranium. Concentrating power was reduced (specific gravity 1.009 to 1.019), and pitressin lost its effectiveness. The inulin/creatinine clearance ratio fell from 1.0 to 0.8 or slightly below (because of the polyuria and hyposthenuria the urea/inulin clearance ratio is difficult to interpret) The authors conclude that the reduction of clearances is attributable to back diffusion of all urinary constituents, and that tubules that are sufficiently damaged to permit any considerable back diffusion of creatinine will also permit, but to a lesser extent, the back diffusion of the larger inulin molecule.

Bobey, Longley, Dickes, Price, and Hayman [300] showed that uranium intoxication can practically abolish the tubular excretion of diodrast; the 'tubular extraction ratio' (corrected for filtration) fell to zero and Tm_D was reduced to low and even negative values. The diodrast clearance was sometimes less than the inulin clearance. Again, the creatinine/inulin clearance ratio fell below 1.0, in 1 instance to 0.55, but no excessive decrease in the urea/inulin clearance ratio was observed. During extreme reduction of the

inulin, creatinine, urea, and diodrast clearances, the renal plasma flow calculated from E_{IN} and E_{CR} was not reduced. The authors suggest that, like creatinine, some of the filtered diodrast escapes from the tubular urine, explaining the negative values of Tm_D. As recovery from poisoning occurs, all clearances return to normal, tubular excretion of diodrast recovering more rapidly than other functions, perhaps because the filtration rate remains permanently reduced in consequence of vascular scarring.

Laake [1183] examined the effects of uranyl nitrate (0.12 to 0.75 mg.) in rabbits. In surviving animals the inulin and diodrast clearances, Tm_D and Tm_G, were reversibly reduced, maximal reduction occurring from the second to the fifth day. Recovery was effected in 10 to 18 days. Proteinuria and glucosuria usually occurred simultaneously on the second or third day. There was no ketonuria. The author concludes that uranium impairs the function of the proximal tubule, and if the injury is sufficient it is accompanied by reabsorption of inulin and all other constituents of the tubular urine.

The inhalation of dust containing uranyl salts in sufficient dosage leads to renal injury in rabbits and dogs similar to acute uranium intoxication, with a marked decrease in diodrast excretion and decreased reabsorption of chloride. In extreme instances filtered diodrast was differentially lost from the tubular urine by back diffusion, as judged by the excretion of inulin.[2227]

After intravenous injection into rats, rabbits, and cats, roughly two-thirds of the dose of uranyl nitrate is excreted in the urine within 24 hr. About a fifth is taken up by bone and mobilized very slowly. Alkali administration appears to promote excretion, acidosis to retard it, but whether this is a renal effect is not demonstrated.[1606]

BAL, which is an effective antidote to mercury, arsenic, and other heavy metals that combine with —SH groups, does not afford protection against uranium [1606] and even sensitizes the renal epithelium to this agent, as in the case of cadmium.[1862]

Uranium intoxication is accompanied by an increased excretion of amino acids, which can be detected quantitatively by determining the amino acid/creatinine concentration ratios in 'spot' samples of urine. The test is apparently sensitive enough to have practical value in detecting early or mild intoxication.[129, 1748]

There can be no doubt that in the uranium-poisoned kidney the renal blood flow remains essentially normal, and that all clearances including the inulin clearance are greatly reduced because of absorption through injured tubules. Diffusion no doubt plays a part in the absorptive process, but it is the difference in oncotic pressure between the tubular urine and the peritubular capillary blood which leads to the gross migration of water, and with it all the urinary constituents, through permeable tubules.

Partial ureteral obstruction also leads to loss of concentrating power and a tendency to polyuria during dehydration. Hayman and his coworkers liken ureteral obstruction to uranium poisoning, although during obstruction renal ischemia, not present in uranium intoxication, may contribute to tubular injury. If the injury from ureteral obstruction is not too severe, tubular function recovers completely in a month or so.[941]

Tartaric Acid

Salts of tartaric acid also exert a toxic action on the proximal tubule, the glomeruli being unaffected and the distal system showing but slight pathological changes. Nicholson, Urquart, and Selby [1625] have examined the effects of tartrate intoxication in one kidney by perfusing that kidney *in situ* with the toxic solution and afterwards re-establishing the natural circulation. Tartrate intoxication was accompanied by a reduction of the urea, xylose, creatinine, inulin, and phenol red clearances. The urea/creatinine clearance ratio was lower on the poisoned side than on the control side, but there seemed to be no consistent dissociation of the creatinine and inulin clearances. In the normal kidney excreting ferrocyanide, this substance could not be demonstrated in the tubule cells, but it is present in the cells of the proximal tubules, indicating injury of sufficient degree to permit back diffusion of all urinary constituents. Chloride excretion was increased, but ammonia formation was not impaired.

Mercury

Mercury also produces necrosis of the proximal tubule. All portions are affected to some extent, but the greatest damage in the human, rabbit, or rat kidney is suffered by the lower portion. Ob-

vious injury to the distal tubule is rarely observed, even with lethal quantities of mercuric chloride, and if the thin limb is affected it is not cytologically observable because of the squamous nature of the epithelium.[874] Severe intoxication with mercury, as with uranium and bichromate, induces glucosuria.[878] Toxic doses of mercury can be antidoted by BAL.[776, 1265]

Organic mercurial compounds block the reabsorption of sodium, a circumstance which forms the basis for their use as diuretics. The action of such compounds is discussed in chapter XXVII.

Bichromate

Bichromate exerts a nephrotoxic action similar to that of mercury and uranium but affecting the early portion of the proximal tubule. In rabbits intoxicated with bichromate, Schou[1000] found that the creatinine clearance was reduced from the range of 12 to 13.6 cc. to the range of 1.3 to 4.3 cc., and the normal creatinine U/P ratio from the range of 250 to 303 cc. to the range of 6.9 to 9.9 cc. The fractions of filtered chloride and urea excreted were increased, but not that of glucose. The creatinine U/P ratio under control conditions was reduced from high values to less than 10. Sulphate diuresis produced a smaller increase in urine flow (1.6 to 10.0 cc.) in intoxicated animals than in normal animals (7.5 to 16.3 cc.). The minimal creatinine U/P ratio during sulphate diuresis was reduced to 1.03, as compared with low values of 1.4 to 1.5 in normal animals; during diuresis the reabsorption of sulphate, urea, and glucose could be reduced to zero, though chloride reabsorption (at creatinine U/P ratios of 1.31 to 1.55) remained at 36 to 53 per cent.

It is of particular interest that in every instance the creatinine clearance increased in these intoxicated animals after the induction of sulphate diuresis (12 to 24, 13.6 to 21.6, 1.3 to 7.2, 3.5 to 8.0, and 4.3 to 10.8 cc.); this increase is consonant with the assumption that the reduction in creatinine clearance following bichromate intoxication is attributable in great measure to back diffusion through the proximal tubules, and that during sulphate diuresis water and solutes including creatinine are to some extent restrained from back diffusion and carried into the bladder urine. The argument falls short of finality, however, because an increase

in glomerular activity when the extracellular fluid is greatly expanded by hypertonic sulphate solution cannot be excluded, the increase in filtration rate being very large in normal animals under these conditions (11.9 to 26.3, 7.6 to 16.3, 9 to 34.8, 12 to 22.5, etc.).[1797,1799]

Tetrathionate

In the dog and rabbit, tetrathionate is rapidly reduced to thiosulphate. Coincidentally there is a nephrotoxic action of such severity that complete anuria results within 30 to 60 min. after the injection of doses which, if injected as equivalent thiosulphate, would be wholly non-toxic. Rapid injury of the proximal tubule is apparently the chief renal lesion, degeneration involving even the nuclei within 30 min. The —SH enzymatic system appears to be involved.[784]

EXPERIMENTAL ACUTE ISCHEMIA

Koletsky and Gustafson [1147] have shown that rats generally survive bilateral clamping of the renal artery for periods lasting up to 1 hr., whereas animals rendered bilaterally ischemic for 2 hr. die in uremia before regeneration is effective. The majority of dogs survive bilateral renal ischemia of 45 min.[1117]

A more informative procedure is that used by Koletsky and Dillon,[1144] who clamped one renal artery in rats and, after 3 weeks to afford opportunity for regeneration of the ischemic kidney, removed the other kidney. By this technique, the mortality was 0, 7, 40, 60, and 87 per cent after ischemia of 1.5, 2, 3, 3.5, and 4 hr., respectively If the ischemic period does not exceed 2 hr., the rat kidney can generally regain enough function to permit survival, but after 3 hr. of ischemia the chance of survival is reduced to about half. Pathological changes in the kidney are followed by rapid repair and at the end of a week the tubules are largely cleared of debris and lined by newly formed epithelium. Progressive renal atrophy then sets in, however, so that at 3 weeks the kidney, although completely repaired, is reduced to approximately one-half or one-third the normal size. This atrophic state persists indefinitely so long as the normal kidney remains in the body, but removal of the normal kidney leads to hypertrophy of the injured organ if the animal survives.

Badenoch and Darmady,[71] removing one kidney and simul-

taneously clamping the other renal artery in rabbits, obtained a mortality of 20, 60, and 100 per cent after clamping for 60, 90, and 120 min., respectively.

Selkurt[1821,1822] found that clamping one renal artery in anesthetized (pentobarbital sodium) dogs was followed, after release of the clamp, by a reduction in both the creatinine and PAH clearances in the clamped kidney. Following 3 to 5 min. of complete ischemia, these clearances returned to the control values within 120 min. Following 10 min. of ischemia, recovery was incomplete within 120 min., the creatinine clearance returning to only 30 per cent of the control, the PAH clearance to 44 per cent. Following 20 min. of ischemia, there was extreme oliguria or anuria for 2 hr.; however, under mannitol diuresis, both clearances were found to have substantial, albeit subnormal, values at 175 min. E_{PAH} was only slightly affected by 3 to 5 min., but was markedly reduced by 10 min. of ischemia. In the 20 min. experiments E_{PAH} was 0.118 without mannitol, and 0.425 when mannitol was used as a diuretic.

In simultaneous observations on PAH clearances and the measurement of renal blood flow by a cannulation method, Selkurt found that the blood flow calculated from the unadjusted P... clearance averaged 91 per cent of that measured directly. Af... 20 min. of ischemia, the total blood flow was reduced by some ... per cent for 85 min. or more, despite maintenance of arterial pre... sure, showing increased renal vascular resistance. E_{PAH} was re... duced from a control value of 0.74 * to 0.56, the ratio of PAH clearance to total blood flow being 0.30 at 37, 0.53 at 58, and 0.83 at 85 min. after release of the clamp. It appears that irreversible tubular injury is not caused by 10 to 20 min. of ischemia, and that substantial recovery of tubular excretion can occur despite persistent reduction in renal blood flow.

With longer periods of ischemia the kidney lost concentrating power, the creatinine U/P ratio at urine flows below 0.15 cc/min. decreasing from an average of 336 to 126. The U/P ratio of PAH was correspondingly reduced; consequently there was a marked correlation between both clearances and urine flow.

* These figures on E_{PAH} are low in Selkurt's experiments because of diffusion of PAH out of the red cell during centrifugation, the normal figure recorded by him being the same as that obtained by Phillips *et al.*[1606] for whole blood

Hamilton, Phillips, and Hiller [896] found that anesthetized dogs with the right kidney removed uniformly survived clamping of the left renal artery for 2 hr. and some survived ischemia of 3 to 4 hr. In dogs subjected to 3 hr. of renal ischemia the mortality was greater during a hot, humid summer than during winter. Death in uremia regularly followed longer periods of ischemia. After the clamp was removed, the urea clearance was extremely low, of the order of 10 per cent of normal, and marked nitrogen retention occurred. If recovery ensued, the urea clearance improved uniformly and eventually reached a normal value, although a month was sometimes required for it to do so.

Though the total blood flow, as calculated from E_{PAH} and the PAH clearance, might return to normal immediately after removal of the clamp, more frequently it remained moderately reduced, the average recovery at 90 to 120 min. for all periods of clamping being 81 per cent. E_{PAH} and E_{CR} were not greatly affected by 20 min. of ischemia, but after 2 hr. of ischemia they were markedly reduced, E_{PAH} from the range of 0.90 to 0.94 to 0.11 to 0.43, and E_{CR} from the range of 0.19 to 0.23 to 0.02 to 0.14.[1607]

Scheibe, Giraldi, and Vermeulen,[1777] using the development of azotemia as their index of renal injury, found that the renal vein can be occluded for 30 min. and the renal pedicle for 90 min. in the rat, or for twice these periods in the dog, without permanent renal damage. Damage was more rapidly effected by occlusion of the renal vein than of the whole pedicle, a fact which may possibly be explained by the presence of greater capillary pressure during venous obstruction.

Semb [1393] reports that during renal resection he has clamped the renal pedicle in man for as much as 1.5 hr., as a rule for 45 min. to 1 hr., without evidence of permanent damage. Malm [1273] reports that in 1 case the renal vessels were clamped for 50 min. and some 25 per cent of renal tissue removed. By the twenty-sixth day after operation this kidney had 50 per cent of the preoperative value for Tm_{PAH}.

It seems to be general urologic opinion, however, that in man the renal pedicle should not be clamped for periods longer than 30 min.

HEMORRHAGIC SHOCK

That a prolonged period of hypotension and shock can lead to irreversible damage of the kidneys, so that death may ensue from uremia at a late date despite recovery from shock itself, was observed by Rogers over 30 years ago in his classic studies of cholera, in which shock is caused by dehydration. The importance of this type of renal failure was recognized in World War II by Bywaters [115] in connection with the crush syndrome, and has led to numerous studies of the renal circulation after traumatic injury in animals and man.

Corcoran and Page [119] induced hemorrhagic shock in anesthetized dogs (pentobarbital) by controlled bleeding, maintaining the arterial pressure at about 60 mm. Hg for some 70 min., followed by transfusion of blood and restoration of blood pressure, this cycle being repeated 2 or 3 times. Diodrast and inulin extraction ratios were determined on dogs with one kidney explanted subcutaneously, the other kidney having been removed. In other dogs renal denervation was performed 7 to 10 days before the experiments. They found that during the period of hypotension the total renal blood flow, as calculated from E_D and the diodrast clearance, or E_{IN} and the inulin clearance, was decreased. Both clearances fell to zero or nearly so at an arterial pressure of about 60 mm. Hg, and at a pressure of 60 to 70 mm. Hg slight changes in pressure were accompanied by marked changes in renal blood flow and filtration rate. During hypotension the true filtration fraction decreased, but it never fell below 0.05.* On restoration of arterial pressure to normal levels by transfusion, the renal blood flow returned temporarily to control values without showing reactive hyperemia; rather it generally tended to decrease again.

During the period of hypotension and immediately after the restoration of pressure, E_D fell markedly, in the first instance, the authors suggest, because of unequal distribution of blood and failure of perfusion in some nephrons, in the second instance because diodrast accumulates in the tubules and interstitial fluid during hypotension. On restoration of the blood flow this accu-

* That the minimal perfusion pressure cannot be less in theory than the minimal filtration pressure in a permeable system containing 'filtrate,' such as the glomerular capillary bed, has been pointed out in chapter XVIII.

mulated diodrast is added to the renal venous blood to such an extent as to produce a negative extraction ratio. Some of this accumulated diodrast is also excreted with a fallaciously high clearance immediately after restoration of urine flow.* The creatinine and inulin clearances, Corcoran and Page conclude on the basis of the identity of these clearances, continue as valid measures of the filtration rate in hypotension but, because of the marked changes in E_D, the diodrast clearance during and shortly after a period of hypotension bears no certain relation to the renal plasma flow.

Repeated reduction and restoration of blood pressure by hemorrhage and transfusion leads to permanent reduction of renal blood flow Because the same phenomenon occurs in dogs with denervated kidneys, the authors believe that this protracted ischemia is attributable to the appearance in the blood of a vasoconstrictor substance or substances (neither adrenalin nor angiotonin) related to shock. But how important this humoral factor is, relative to neurogenic vasoconstriction, in the production of the ischemia is not determined. They state that renal denervation appears actually to retard and limit the restoration of renal blood flow subsequent to transfusion in the later stages of shock.

Phillips, Dole, Hamilton, Emerson, Archibald, and Van Slyke[1108] found that rapid, massive hemorrhage in dogs anesthetized with nembutal is accompanied by almost complete cessation of renal blood flow as calculated from the PAH clearance and the extraction ratio, presumably owing to renal vasoconstriction, if the fall is below a level which may vary from 60 to 100 mm. Hg. If hemorrhage is not too great, the arterial pressure soon rises as a result of extrarenal vasoconstriction, and the renal blood flow is reestablished but at a figure less than before hemorrhage. In this recovery phase, the kidneys appear to be favored at the expense of the rest of the circulation. The cycle of sudden hemorrhage, drop in blood pressure, renal ischemia, and subsequent partial restoration of blood pressure and renal function can be repeated two or more times in the same animal, until the limit of tolerated blood loss has been reached. Even then, restoration of blood pressure and partial renal function may be accomplished, at least tem-

* The renal dead space introduces large errors in such experiments and makes their interpretation difficult

porarily, by the injection of a volume of blood or plasma equal to only a fraction of what has been lost, apparently because reduction of the volume of the vascular bed by peripheral constriction permits a small quantity of blood to restore an effective circulating blood volume. Where blood depletion persists too long, replacement of all the lost blood causes only a temporary rise in blood pressure and in renal blood flow. Peripheral constriction is replaced by peripheral dilatation and renal function fails again.

In these experiments E_{PAH} remained at 0.87 to 0.84 until the *renal plasma flow fell below 7 cc/min., or about 3* per cent of normal. At lower renal plasma flows, E_{PAH} was reduced and the clearance no longer reflected the renal plasma flow, though the absolute error is slight because the total flow is so small. It is also in this range that Corcoran and Page observed a marked reduction in E_D.

The true filtration fraction, as calculated from E_{CR}, did not decrease *pari passu* with decreasing renal plasma flow or with the systemic blood pressure. In fact, it sometimes increased when the renal plasma flow was falling, indicating predominance of efferent arteriolar constriction over afferent constriction, which was also marked.

Ultimately, peripheral constriction fails to maintain systemic pressure and the renal plasma flow and filtration rate fall to low values. Renal failure may be reached even though the systemic pressure is still at a level of 60 to 100 mm. Hg. It is inferred that at this stage afferent vasoconstriction shuts off the renal circulation entirely in an effort to maintain the circulation to vital centers.

The effects of muscle trauma appear to be similar to those of hemorrhage, except for the absence of the early, transitory decrease in blood pressure and renal function which accompanies rapid limited hemorrhage. The ultimate reduction of blood pressure that follows trauma proved to be less reversible than hemorrhagic hypotension.

The normally small oxygen arterial-venous difference characteristic of the kidney remains small in early hemorrhagic shock despite a marked decrease in renal blood flow. Consequently, the oxygen consumption decreases almost in proportion to the renal

blood flow. This is in marked contrast to the rest of the body, which maintains its oxygen consumption, and hence increases the systemic oxygen arterial-venous difference as the cardiac output decreases.[631]

In standardized hemorrhagic shock induced by controlled bleeding in dogs under pentobarbital anesthesia, Selkurt [1823] found that when the mean blood pressure was lowered to 60 mm. Hg the renal blood flow as measured directly by a cannulation procedure decreased immediately to some 40 per cent of the control value, while reduction of pressure to 40 mm. Hg reduced renal blood flow to about 11 per cent of the control value. In both conditions, but particularly at the lower pressure, renal vascular resistance, as calculated from mean pressure and total renal blood flow, increased gradually, resulting in a further decrease in renal blood flow. Late in the 60 mm. period E_{PAH} might be reduced to low values and might even become negative, i.e. the concentration of PAH in the renal venous blood might be greater than in the arterial blood. He attributes this phenomenon to the reabsorption of PAH from the tubular urine, but it may be explained, as Corcoran and Page [419] suggest, by absorption into the renal venous blood of PAH accumulated in the interstitial fluid during the period of hypotension. During hypotension no urine is formed, even though appreciable quantities of blood are flowing through the kidneys.

Upon reinfusion of blood there was an immediate, though not complete, restoration of renal blood flow. With a return of mean blood pressure to 70 to 80 per cent of the control figures, renal vascular resistance decreased to approximately the control value. E_{PAH} rose toward normal, but later decreased again to lower values The creatinine clearance also remained reduced to a greater extent than would be expected from the existing blood pressure and renal blood flow. Although Selkurt believes that his observations indicate the back diffusion of creatinine, the alternative explanation of reduced glomerular pressure may be involved. The creatinine U/P ratio was markedly reduced even during oliguria, as a result of either back diffusion or loss of concentrating power.

TOURNIQUET SHOCK AND BURNS

Allowing for the time factor and sequence of events, the changes induced in renal function by tourniquet shock in dogs are much the same as are observed after hemorrhage. Corcoran, Taylor, and Page [429] report that, shortly after the application of a tourniquet to the leg at such a pressure as to stop venous outflow without blocking arterial inflow, the renal blood flow and filtration rate begin to decrease, and by 90 min. level off at about 25 per cent of the control values. The arterial pressure falls about 25 per cent and the hematocrit increases substantially, but neither of these factors appears to be responsible for the decreased renal function, which the authors attribute to renal vasoconstriction. During this period E_D is not reduced. On release of a tourniquet which has been in place for some 200 min., the blood flow may recover momentarily only to fall again to low levels if shock supervenes If shock does not occur, a slow recovery is effected. With the development of shock, E_D falls to about 0.50. The infusion of blood during or after the application of the tourniquet does not materially alter the course of renal events.

In dogs with previously denervated kidneys the reduction of renal blood flow and filtration rate during and after the application of the tourniquet is less marked, but still to some 50 per cent of the control level. The authors inferred originally that nervous stimulation, presumably excited by pain, is responsible for some measure of the vasoconstriction, but that the major effect is independent of the renal nerves, and is, by exclusion, of humoral origin. A peripheral vasoconstrictor substance was demonstrated in increased amounts in the blood in all animals except one, a hypertensive dog which showed only a slight depression in renal blood flow. This substance may be serotonin, a pressor substance associated in some way with the blood platelets.[1566, 1682] Subsequently, however, new experiments led Taylor and Page [2055] to believe that the renal vasoconstriction is mediated neurogenically during the onset of tourniquet shock, and that only the later vasoconstriction involves humoral factors.

Eggleton, Richardson, Schild, and Winton [587] studied the effect of tourniquet application and crushing of the hind limbs of anes-

thetized (nembutal) dogs, the tourniquets being left in place for 4 to 5 hr. Immediately upon release of the tourniquet the arterial pressure fell and urine flow, which had been well maintained, ceased. Restoration of pressure by gum acacia solution led to return of urine flow; the creatinine clearance returned to only about one-third of the control value. Osmotic diuresis increased the urine flow and creatinine clearance but the latter did not return to normal. The authors recognized several possibilities in the sequence leading to reduced renal function, and believed that they could exclude the following: renal edema, tubular obstruction by cast formation, closure of glomeruli, and poisoning of the renal tubule by humoral agents. They believed that they could exclude anoxic injury of the tubules because renal function was not impaired following 30 to 60 min of arterial hypotension (30 to 50 mm. Hg) or anuria induced by the intravenous infusion of histamine, and that they could exclude reduced glomerular pressure as a causal factor because post mortem the glomeruli were well filled with blood and in the post-traumatic oliguric period the creatinine U/P ratio was low rather than high. In their opinion no single hypothesis explains the oliguric state. In the absence of data on renal blood flow during histamine infusion, these experiments do not argue too strongly against anoxic injury of the tubules. However, it is difficult to explain why the creatinine U/P ratio should be low (9 to 14) in the oliguric period immediately after removal of the tourniquet. This is the time when, by their evidence (creatinine clearance), renal vasoconstriction has just set in and there should have been no time for injury of the tubules. Admittedly, the oliguria in the experiments of Eggleton and her coworkers is difficult to understand, and the differences between their experiments and those of Corcoran, Taylor, and Page require reconciliation.

A reduction of renal blood flow in cats suffering from tourniquet and hemorrhagic shock has been demonstrated by Keele and Slome,[1098] using direct or plethysmographic methods. No functional data are reported.

Dziemian[556] reports that, in goats with severe third-degree burns covering about 50 per cent of the body surface, renal plasma flow, filtration rate, and glucose Tm may be markedly reduced.

injury, 7 cases, all of whom were in coma and died shortly after study. This group with head injury was not in shock and stands in sharp contrast to the others.

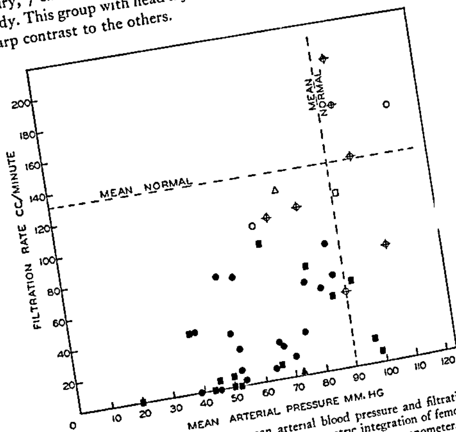


FIGURE 137. Relationship between mean arterial blood pressure and filtration rate. Mean arterial pressure was obtained by planimetric integration of femoral pressure pulse tracings recorded by means of a Hamilton type manometer. In most shock cases, the decrease in filtration rate is greater than the corresponding decrease in mean arterial pressure. (Lauson, Bradley, and Cournand[111])

The filtration rate (fig. 136) and renal blood flow were reduced in practically every case where shock was present, the reduction roughly paralleling the degree of shock (fig. 137). On the other hand, renal function in patients not in shock fell within the normal range. The filtration fraction in patients with shock was distributed equally above and below the average normal value of 19 per cent. In 5 of the 7 cases of head injury, the filtration fraction was

relatively high (20 to 27 per cent), possibly because of elevated blood pressure (fig. 136).

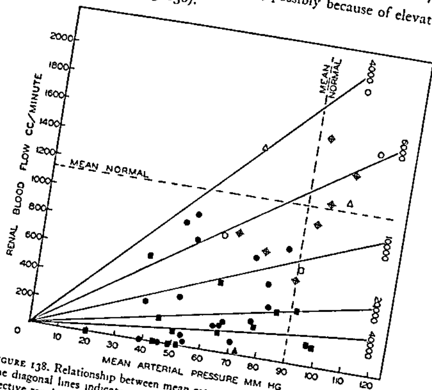


FIGURE 138. Relationship between mean arterial pressure and renal blood flow The diagonal lines indicate successive values, expressed in absolute units, for effective renal vascular resistance

$$\left(R_K = \frac{Pm}{RBF}\right)$$

The normal range is approximately 4000 to 10,000 absolute units In most shock cases, the points lie in zones of increased resistance, indicating renal vasoconstriction (Lauson, Bradley, and Cournand 111)

The diagonal lines in figure 138 define various levels of renal vascular resistance, computed as $R = Pm \times 1332$/renal blood flow in cc/sec.* If the renal blood flow decreased in proportion to the reduction in blood pressure, the regression of R would fall

* The figure 1332 should be 1328

within the normal range of 4000 to 10,000 absolute units. On the contrary, most values representing patients in shock are found in

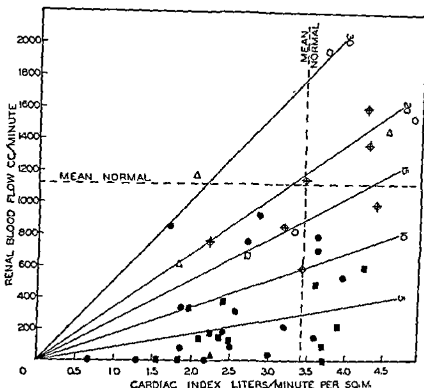


FIGURE 139. Relationship between cardiac output in l/min. per sq. m. and the renal blood flow in cc/min per 1.73 sq m body surface area. Cardiac output was measured by the direct Fick method. The diagonal lines indicate successive values of the renal fraction, expressed as per cent, calculated on the basis of cardiac output per 1.73 sq. m. In normal man, under similar technical conditions, about 15 per cent of the cardiac output flows through the kidneys (the normal basal figure is probably closer to 20 per cent). In most shock cases the renal fraction was considerably less than normal, indicating that as the cardiac output decreased blood was shunted away from the kidneys (Lauson, Bradley, and Cournand[1117])

zones of markedly increased renal resistance, indicating the presence of renal vasoconstriction.

The relation between renal blood flow and cardiac output is shown in figure 139. Here the diagonal lines indicate increasing values of the renal fraction (the fraction of the cardiac output

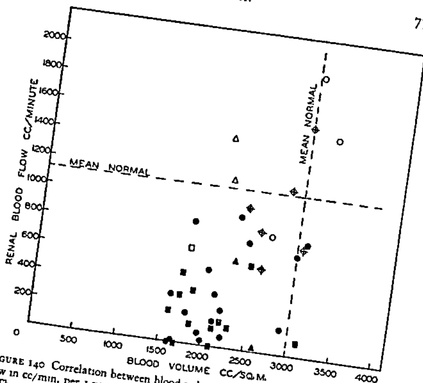


FIGURE 140 Correlation between blood volume in cc/sq. m. and the renal blood flow in cc/min. per 1.73 sq m of body surface area

The correlation is improved somewhat by the deletion of the 3 points in the lower right-hand corner of the chart In the first (indicated by the square), the last blood volume measurement was made more than 3 hr. before the clearance study, and since the patient's blood pressure and general condition had deteriorated during that time, it is probable that further blood loss had occurred The second (indicated by the solid triangle) had suffered from strangulated hernia for 4 days and it is probable that toxic and infectious factors in addition to loss of body water contributed to his collapse The third dot represents the initial observation on a patient in whom severe acute alcoholism may have caused a marked fall in blood pressure in spite of the fact that the cardiac output and blood volume were near normal. Even including these 3 observations, there is a fair correlation between blood volume and renal blood flow. (Lauson, Bradley, and Cournand [111])

flowing through the kidneys). In only one case where shock was present was the renal fraction greater than the average normal of 19 per cent.* This great reduction in renal fraction indicates the extent to which renal vasoconstriction shunted blood away from the kidneys to other parts of the body. Here again the head injuries present a marked contrast to shock; in these patients the kidneys continue to receive their full complement of blood.

A priori, a correlation between blood volume and renal blood flow would be expected on the basis of the oligemic origin of traumatic shock. Figure 140 shows that most of the values representing patients in shock fall below the normal range of blood volume, though the correlation with renal blood flow is not as striking as in the case of blood pressure and cardiac output.

The development of uncompensated acidosis during shock suggests a possible causal relationship to reduced renal function, especially in view of the alleged role of acidosis in renal injury in other forms of dehydration.[2092] The lowest renal blood flow values were in fact associated with the lowest blood pH values, but the Bellevue study shows that marked reduction in renal blood flow can occur in the presence of a normal blood pH (fig. 141). Moreover, the renal blood flow is apparently reduced promptly following injury or hemorrhage, whereas acidosis due to organic acid accumulation depends on the duration and degree of shock, and renal blood flow may be increased by therapy while the blood pH continues to fall. Hence Lauson and his coworkers conclude that acidosis is not the cause of the decrease in renal blood flow. On the contrary, renal ischemia probably augments the acidosis resulting from widespread tissue anoxia, both by removing the mechanism for fixed acid excretion and by removing a locus of organic acid oxidation.

Oliguria was observed in nearly all patients with shock. In some of the most severe cases, transient complete anuria occurred, and not until the general circulation had improved as a result of treatment did the urine flow return to measurable values Anuria in shock appears to indicate almost complete arrest of the renal circulation, since urine is still formed when the diodrast clearance is

* The figure 19 per cent represents the average normal value used by these investigators A larger series of determinations is discussed in chapter XVII.

of the order of 5 to 10 per cent of normal. When mannitol was used as a diuretic, the U/P ratio of this compound remained relatively fixed (average 37) over a wide range of filtration rates, so that V was a linear function of the filtration rate (fig. 142). Under these conditions the maximal urinary concentration of mannitol is about

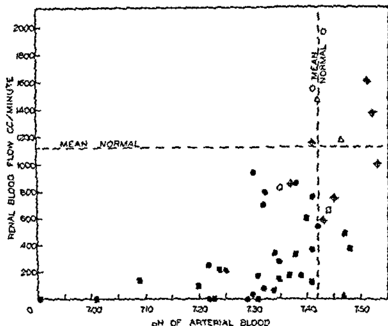


FIGURE 141 R[illegible] flow. Note th[illegible] blood pH, a [illegible] is the primary cause of renal [illegible] in shock. (Lauson, Bradley, and Cournand [137])

4 to 5 per cent, which is approximately isosmotic with plasma, implying that the distal tubule has lost its concentrating power; * † since the quantity of mannitol delivered to the tubules (at a roughly constant plasma concentration) is proportional to the filtration rate, the urine flow will vary with the mannitol load and

* The authors incorrectly speak of this as the limiting osmotic pressure of the urine.

† The same relationship would result if only a few nephrons were active and if the mannitol set up osmotic diuresis in these few active nephrons [illegible]

hence with the filtration rate. In the absence of mannitol (i.e. where only inulin was used) there was no close correlation between filtration rate and urine flow, except that low values of one occurred with low values of the other.

Skeletal trauma and hemorrhage, when followed by shock, were accompanied by much the same changes in renal function. The tendency toward high filtration fractions after head injury has been noted. The data suggest that, in shock following burns, the filtration rate is maintained or is abnormally high, yielding a high filtration fraction which persists even when renal blood flow is greatly reduced. The impression is recorded that acute alcoholism complicating slight or moderate oligemia results in generalized vasodilatation which is reflected in the kidney by a lower filtration fraction and larger renal blood flow than would be expected otherwise with similar levels of blood pressure.

After the transfusion of blood or plasma the filtration fraction tends to increase. The filtration rate increases as the arterial pressure rises, but after a temporary increase the renal blood flow tends to remain low or to fall to still lower values. Although a reduction in E_{PAH} as a result of prolonged reduction in renal blood flow cannot be excluded, the data suggest that renal vasoconstriction persists after restoration of blood pressure. In all cases examined several weeks after recovery, both the filtration rate and renal blood flow had returned to the normal range.

It should be observed that no cases of post-traumatic anuria were observed in this study, possibly because of the promptness with which therapy was instituted. No information is available on intravascular hemolysis, but it is reasonable to assume that there was as much intravascular hemolysis in the traumatic and burn cases studied by Lauson *et al.* as in other instances where post-shock anuria has supervened.*

The investigation confirms the generally accepted view that the urinary changes in shock, namely oliguria or anuria and loss or impairment of concentrating power, are the result of renal ischemia. This reduction in the renal circulation is of considerable

* [illegible] of mannitol in clearance studies, [illegible] mission, may have reduced cast [illegible] by osmotic diuresis.

importance for the maintenance of the systemic circulation For example, in one case of trauma the total blood volume was reduced 30 per cent below the average normal value; the cardiac output decreased from an estimated (normal) value of 5.30 liter/min. to

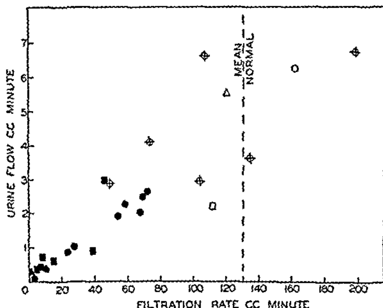


FIGURE 142 Correlation between rate of filtration and urine flow in all cases in which mannitol was used to measure the filtration rate. This high degree of correlation is a consequence of the osmotic diuretic action of the mannitol used for measuring the filtration rate. (Lauson, Bradley, and Cournard [397])

3.75 liters, a reduction of 29 per cent; at the same time the renal blood flow was reduced from an estimated (normal) value of 1000 cc/min. to 160 cc., thus a quantity of blood equivalent to two-thirds of the reduction in cardiac output was made available to the systemic circulation by renal vasoconstriction. The mechanism of this vasoconstriction, whether neurogenic or humoral, is undetermined. It seems probable that both the renal sympathetic fibers and adrenalin as well as other humoral factors play a part. It is definitely to be concluded that, despite its autonomy under ordinary circumstances, the renal circulation in man is subordinate to the welfare of the body as a whole.

In a smaller series of patients examined at the Italian Front, Burnett, Shapiro, Simeone, Beecher, Mallory, and Sullivan [300] similarly observed that after severe traumatic injury the filtration rate and PAH clearance are reduced, and in about the same proportion. Significant reduction was sometimes present without clinical signs of shock. A noteworthy feature of these data is the indication that, in the renal ischemia produced by injury short of shock, the proximal tubule remains uninjured, as judged by Tm_{PAH}. This function was reduced substantially below normal in only 3 out of 11 patients studied. One of these was classified as having initially had severe shock, 1 moderate shock, and 1 had never been in shock. In the remaining 8, Tm_{PAH} was normal or supernormal. Tm_{PAH} was normal in 1 patient who was studied 20 hr. after wounding and while in severe shock, despite a low filtration rate (79 cc.) and PAH clearance (381 cc.). Recovery of Tm_{PAH} was observed in all 3 patients mentioned above; in 1 this function increased from 7 to 90 mg. between the eleventh and the forty-ninth day after injury, the PAH clearance increasing from 99 to 688 cc. In 9 out of 11 cases the C_M/Tm_{PAH} ratio was normal or low, indicating functional reduction of glomerular activity without parallel injury of proximal tissue.

One patient died in uremia 8 days after wounding, despite the fact that on the third day the filtration rate was 89 cc., the PAH clearance 598 cc., and Tm_{PAH} 108 mg. A second patient is stated to have died in uremia(?) 9 days after injury, despite the fact that 16 hr. before death the filtration rate was 64 cc., the renal plasma flow 356 cc., Tm_{PAH} 70 mg., N.P.N. 99 mg/100 cc., and the urine output on the day of the test 1558 cc.

The authors point out that the ability to produce a concentrated urine may diminish during shock and improve rapidly over a period of 3 to 7 days, unless renal failure is severe, when concentrating power may be impaired for many days and remain low even after the filtration rate, effective renal plasma flow, and Tm_{PAH} have returned to normal.

Sanderson [1767] reports one subject who was examined 24 hr. after aortic embolectomy and 8 hr. before death, at a time when the blood pressure was good but surgical shock was probably impending. The filtration rate was 23 cc. and the diodrast clearance

60 cc. Another patient examined on the [illegible] costomy for strangulation, with intestinal perfor[illegible] abscess, peritonitis, and empyema, showed a [illegible] clearance of 174 cc. and a diodrast clearance of [illegible] fraction = 0.35). The urine was consistently [illegible] a normal plasma chloride (96 to 110 mEq/liter). [illegible] of a high filtration rate with abscess and other [illegible] noted (see ch. XXIII). A third patient suffering fr[illegible] dehydration, external discharge of bile, periton[illegible] and peritonitis, examined 1 month postoperativ[illegible] fore death, had an inulin clearance of 11 cc. and [illegible] ance of 76 cc. Although the blood volume was [illegible] reduced, there was little clinical evidence of [illegible] time of the examination, and Sanderson inter[illegible] renal function as indicative of damage incurred [illegible] dehydration, associated with loss of base throu[illegible] charge and consequent reduction of plasma vo[illegible] tient with intestinal obstruction uncomplicate[illegible] with a marked reduction in blood volume show[illegible] ance of 34 cc. and a diodrast clearance of 281 cc[illegible] after correction of the obstruction, these figu[illegible] cc., showing essentially complete restoratio[illegible] The author accepts the interpretation that [illegible] in these cases is probably attributable to ren[illegible]

Wilkins, Culbertson, Burrows, Tinsley, Jud[illegible] have shown that, when the legs of supine su[illegible] by blood-pressure cuffs inflated on the thigh[illegible] pressure for 10 to 20 min., there was usual[illegible] terial pressure or pulse rate, and little effect [illegible] function. However, 10 to 20 min. after the re[illegible] cuffs there was a marked antidiuresis, a d[illegible] cent) in renal plasma flow (PAH) and filtra[illegible] nitol), and a reduction of sodium, potass[illegible] cretion (as much as 60 per cent). In 10 to [illegible] renal circulation and electrolyte excretio[illegible] peared, but the antidiuresis persisted for [illegible]

Similar renal functional and circulatory [illegible] congestion of the limbs of hypertensive su[illegible]

lumbodorsal sympathectomy, so that the effect is apparently not mediated by the sympathetic nervous system. The authors suggest that the venous congestion is pertinent to cardiac failure, where increased venous pressure may lead to venous congestion of the limbs (and of other organs), but the experiments quoted indicate that renal effects become manifest only when the congestion is relieved.

CHEMICAL INTOXICATIONS

Redish, West, Whitehead, and Chasis [1686] report on a patient who developed 4 days of anuria and 5 days of oliguria during sulfathiazole chewing-gum intoxication. Two weeks after the onset of anuria and at the end of the oliguric period the mannitol clearance was 17.2 and the PAH clearance 14.6 cc.; Tm_{PAH} had a negative(?) value of -1.1 mg. A week and a half later the mannitol clearance was 75.0 and the PAH clearance 220.4 cc., but Tm_{PAH} still had a negative (?) value of -9.4 mg. Progressive recovery ensued until at about 8 months the mannitol clearance was 91.0 and the PAH clearance 586 cc., and Tm_{PAH} 85.6 mg. The last two figures may be considered as normal, the first nearly so. The azotemia, which reached a peak of 214 mg/100 cc. NPN 5 days after the onset of anuria, may be referred either to reduced filtration rate or back diffusion; the effect in either case is to reduce the net urea clearance. If back diffusion is accepted, the filtration rate and renal blood flow immediately after diuresis may, of course, have been considerably greater than the data indicate.

Marshall and Hoffman [1389] report on 3 patients recovering from anuria; one, following postpneumonia shock, was oliguric for 10 days; the second, following postpartum hemorrhage and shock, was oliguric for 5 days; and the third, following carbon tetrachloride poisoning, was oliguric for 8 days. In all 3 the urea, mannitol, and PAH clearances had very low values in the immediate postoliguric period but recovered in a parallel manner to reach normal values, in the first 2 patients some time after 50 and before 200 days, in the third within 2 to 3 months. As in the case studied by Redish *et al.*,[1686] the first 2 patients showed initially a negative(?) Tm_{PAH} (-6.1 and -3.1 mg.), but in all 3 this function recovered to the mean normal value. Marshall and Hoffman accept

that the primary renal disturbance is protracted renal ischemia, and that the major renal defect so produced is injury of the distal(?) tubule, leading to increased permeability and back diffusion of tubular urine. They note that at the onset of diuresis the urine still has a specific gravity close to 1.010, with low U/P ratios of all excretory products, a fact which they attribute to the return of filtration in the absence of concentrating power in the distal tubule.

Corcoran, Taylor, and Page [430] report on a patient suffering from inhalation carbon tetrachloride poisoning, with 4 days of oliguria. In the first observation, made 6 days after the return of urine flow, the inulin clearance was 5.8 cc. and the diodrast clearance 67.8 cc., Tm_D being 3.7 mg. Successive observations showed gradual recovery of clearances, until on the 64th day after the onset of the intoxication, the inulin clearance was 128 cc., the diodrast clearance 649 cc, and Tm_D was 65 mg, all normal figures. Because of the abnormally low initial filtration fraction (0.086) the authors suggest that renal edema, by increasing renal interstitial pressure, impeded the formation of glomerular filtrate.

Sirota [1903] reports on 4 subjects with inhalation carbon tetrachloride poisoning who suffered 2(?), 10, 11, and 17 days of oliguria (fig 143) Two of these showed a marked reduction of E_{PAH} (0.034 and 0 106) and of E_{IN} (0 00 and 0.045), and in total renal plasma flow (24.5 and 160 cc.) in the first observations made 1 to 2 weeks after the onset of oliguria. The other 2 subjects were less severely affected Sirota concludes that late anuria or oliguria in carbon tetrachloride poisoning, and the reduction of all clearances during the period of early diuresis, are the result of renal ischemia, tubular injury and back diffusion He divides the recovery process into three phases. The first starts with the cessation of oliguria and is associated with a continuing increase in plasma creatinine and urea concentrations in spite of diuresis. He believes that this initial phase of diuresis is a result of the re-establishment of selective tubular impermeability or of a slight increment in filtration rate or a combination of both The urine is dilute, contains protein, pigmented casts and red blood cells, and has a specific gravity close to 1 010. The ability to reabsorb chloride is retained, as shown by chloride U/P ratios less than 1.0. But that proximal re-

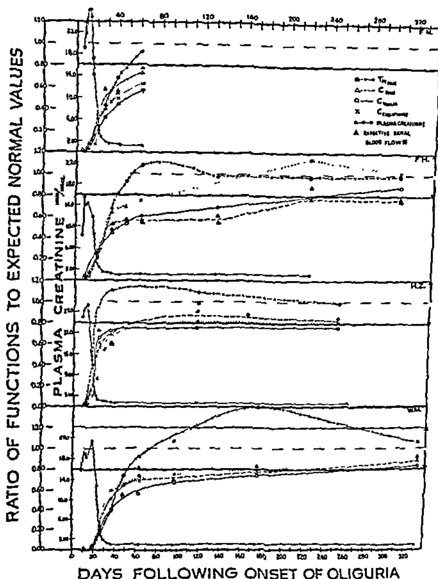


FIGURE 143. Postoliguric recovery of renal function in 4 subjects with carbon tetrachloride intoxication Cessation of oliguria (300 cc/day or less) occurred in F. M. on the tenth day, in F. H. on the third day, in H. Z. on the eleventh day, and in W. M. on the seventeenth day after intoxication. (Sirota [1202])

absorption of sodium has been greatly diminished is indicated by inulin U/P ratios (1.38 and 2.51) far below the minimal value (8 0) typical of the normal kidney. This stage may last from 2 to 8 days. The second phase is marked by a rapid decline in plasma creatinine and urea concentrations simultaneously with a rapid increase in clearance values, the latter reaching 40 to 70 per cent of normal by the 40th day. During this phase, albuminuria, urinary casts, and fixation of specific gravity disappear, and phenol red excretion, E_{PAH}, and Tm_{PAH} return to normal or near normal values. The third phase, starting about the 40th day, is associated with gradual increments in renal plasma flow and filtration, which reach low normal values between the 100th and 200th day. In this phase Tm_{PAH} may reach high normal or supernormal values, which subsequently decline to the expected norm as though there were a transient overdevelopment of tubular tissue. The last function to return to normal is the ability to elaborate a maximally concentrated urine Because of greater variability in reabsorption and rate of formation, plasma urea concentration during the development and recession of azotemia affords a poorer index of glomerular function than does the endogenous creatinine chromogen level

There was no correlation between the speed of recovery and the duration of oliguria or the maximal plasma concentration of creatinine or urea in the studies above The patient who suffered marked oliguria for 11 days recovered most rapidly, while the one who had questionable oliguira for 2 days suffered as severe renal damage as did 2 who were oliguric for 10 and 11 days.

These studies were initiated during late oliguria and early recovery The fact that renal ischemia is present at this late stage throws no light on the initial cause of renal damage Observations are needed before the onset of vomiting and dehydration and before oliguria appears

Sirota believes that the onset of anuria in acute renal failure is attributable primarily to tubular damage and reabsorption of all constituents of the glomerular filtrate. This initial tubular damage may be attributable to severe ischemia (shock kidney, excessive vomiting and dehydration), to primary nephrotoxic effects (carbon tetrachloride, mercury or uranium poisoning), or to a

bination of both (crush syndrome, transfusion reaction). The ischemia of late oliguria as observed in his carbon tetrachloride studies he attributes primarily to the accumulation of inflammatory edema and cellular swelling.

The negative values for Tm_{PAH} reported by several investigators have been interpreted as indicating that not only is there failure of PAH excretion by the tubules, but also some of the PAH which is filtered is lost from the urine. One must infer from this that PAH is more diffusable through the injured tubule than is mannitol or inulin, but the inference is scarcely warranted at this time since such small negative values for Tm_{PAH} might arise, in the complete absence of tubular excretion, from slight errors in the assumed value for plasma protein binding (FW) or in the measurement of the filtration rate. Further data are needed before this point receives a final interpretation.

POSTABORTION ANURIA, ETC.

Humphrey and Jones [1054] report 4 cases of anuria following abortion. Estimates based on two-thirds times the endogenous creatinine chromogen indicate a reduction of the filtration rate to very low values in 2 patients for a period of over 2 weeks, with rapid restoration to only moderately subnormal values within 2 to 3 weeks of diuresis. The urine flow returned to normal (2 liter/day) before the filtration rate. There was no evidence of intravascular hemolysis on careful examination in 2 of these patients, and the histories indicate an uncomplicated vasomotor anuria.

Bailey and Rubenstein [74] report a case of cardiac resuscitation after 30 min. absence of spontaneous heart beat. Renal insufficiency with uremia followed, with eventual recovery. The authors attribute the renal damage to renal anoxia, but the patient had been transfused.

'REFLEX' ANURIA

Frequent reference is made in the clinical literature to 'reflex anuria,' especially in connection with ureteral catheterization or operative manipulation of the genito-urinary tract. Reflex anuria has rarely been observed following hundreds of bladder catheterizations and dozens of ureteral catheterizations carried out by the writer's colleagues. When it did occur it was invariably rapid in

onset and disappearance.* Surgical manipulation of the kidneys, ureters, and adjacent tissues seems more apt to cause reflex stimulation of a degree to initiate clinical anuria, but it is questionable whether such reflex stimulation alone, without continuing irritation or complication, can lead to persistent anuria. It consequently appears that anuria of sufficient duration to become clinically manifest rarely occurs as a response to acute reflex stimulation; the diagnosis is one of exclusion where renal disease, systemic disturbances associated with shock, infection, intravascular hemolysis, or continued irritation must be eliminated as initiating or perpetuating mechanisms.

BACK DIFFUSION

Selkurt[1821] and Phillips and Hamilton[1407] concluded that the reduction in E_{PAH} and E_{CR} in the ischemic kidney is attributable to back diffusion through injured tubules, and oliguria to back diffusion of water. This interpretation is frequently placed upon other data by investigators concerned with impaired renal function in man. It is apparent that the loss of normal tubular impermeability, particularly of the distal system, establishes appropriate conditions for back diffusion if normal nephron architecture, glomerular filtration, and peritubular circulation are preserved. However, this combination of circumstances probably occurs only rarely. Moreover, the physiologic consequences of severe renal ischemia are difficult to distinguish from back diffusion *per se*.

Reduction in E_{PAH} may result simply from loss of excretory power in the proximal tubule as a result of anoxia. Reduction in E_{CR} (and in urine flow) may result from reduction in filtration rate as a result of vasoconstriction and reduction in glomerular pressure, and will, of course, lead to azotemia. All these changes may occur without involving back diffusion. It is consonant with the evidence on the proximal reabsorption of sodium and water

* Ogden and Gaudino, in unpublished observations made in the writer's laboratory, tried ureteral catheterization in female dogs and found that reflex renal ischemia is much more easily invoked in this species than in man, apparently because of the angle at which the ureters enter the bladder. The results were so frequently bizarre that the technique was temporarily abandoned.

to believe that, if the filtration rate is greatly reduced, water reabsorption may continue in the proximal tubule to such an extent that very little urine will be delivered to the distal system. Indeed, proximal sodium and water reabsorption will be limited only by the presence of osmotically active substances such as urea (most of which will diffuse back), creatinine, phosphate, and sulphate, or artificially introduced substances such as mannitol or PAH. Osmotic (mannitol) diuresis will increase all clearances by retarding *proximal reabsorption. If the concentration gradient against which* the tubular excretion of PAH occurs has some upper limit,[1858] proximal oliguria may decrease, and proximal diuresis may increase E_{PAH}. Continued reabsorption of sodium (and water) by the distal tubule will contribute to the oliguria; anoxic injury will impair the concentrating power of the distal tubule so that such urine as is formed will be isosmotic with the plasma. Under these conditions all U/P ratios will be relatively low (perhaps no higher *than 20) and all clearances will vary with the urine flow and be in*creased by osmotic diuresis.

That Phillips *et al.*[1806] found that E_{PAH} remains normal until the renal blood flow is reduced to 3 per cent or less of the normal value in acute experiments shows that there is no back diffusion of PAH at the onset of the renal ischemia associated with hemorrhagic and traumatic shock. After protracted ischemia, lasting 24 *hr. or more, the situation may be different;* degeneration of tubules may then permit selective back diffusion of small molecules or even gross reabsorption of tubular urine.

There are only a few circumstances, apart from the action of *nephrotoxic agents, in which the evidence conclusively points to* back diffusion. Shannon and Winton[1869] observed in the pump-lung-kidney preparation *that*, as the urine flow decreased, the creatinine/inulin clearance ratio decreased from 1.0 to 0.80 or below, and they attributed this to back diffusion of creatinine. The critical factors were apparently the U/P ratio of inulin, i.e. the degree of concentration of the tubular urine, and the rate of urine flow.* The ratio was restored to 1.0 during urea or sulphate di-

uresis. Here one is inclined to place the locus of the back diffusion of creatinine in the distal tubule, where the U/P ratio is maximal and the rate of urine flow critical. Back diffusion appears to occur in certain instances of acute nephritis, largely during the hyperemic phase, as indicated by abnormally low urea/inulin clearance ratios (Earle, pers com.), and in diabetic coma,[1304] where both the urea and creatinine clearances may be low relative to the inulin clearance.

Govaerts notes, in the *Festschrift for Thomas Addis*,[335] that at the peak of intoxication with mercury and bismuth in man and uranium and oxalate in the dog, the urea/creatinine clearance ratio may have a value close to 1.0, indicating almost free permeability of the tubules. During recovery, the creatinine clearance increases more rapidly than the urea clearance, indicating a phase where there is preferential back diffusion of urea with, doubtless, some loss also of creatinine and other constituents.

But until further data on simultaneous clearances are available indicating differential diffusion of small molecules, back diffusion is more of a gratuitous inference than established fact. The ultimate consequences of protracted renal ischemia on the one hand, and of back diffusion with a well-maintained renal circulation and filtration rate on the other, may be identical for the anuric patient, but the implications with respect to genesis and therapy are quite different It will, moreover, be difficult to distinguish back diffusion from the normal but excessive reabsorption of sodium and therefore of water in the proximal tubule under conditions of marked reduction in the filtration rate. Experiments of Harrison and his coworkers[920] demonstrating continuing filtration and proximal reabsorption in nephrons obstructed by hemoglobin casts are cited later in this chapter.

Were back diffusion the only factor in oliguria, one would expect to observe a substantial blood flow accompanying the reduced extraction ratios of all substances. Such is the picture presented by uranium nephrosis (*vide supra*), and it may be noted

patients in diabetic coma, the only one that showed a normal creatinine/inulin clearance ratio had low inulin U/P ratios (7.4 to 22 3), the other 4 had U/P ratios ranging from 38 to 314 This would indicate that the distal tubule is the site of the back diffusion

that this, like all other nephrotoxic agents so far studied, injures the proximal tubule and has little or no discernible effect on the distal tubule. But the situation presented in experimental animals and man during oliguria stemming from shock, etc., is rather different. The total renal blood flow accurately calculated from extraction ratios is generally reduced, sometimes to very low levels, and functional ischemia appears to be the dominant factor. The cause of this ischemia is at the moment unknown.

HEPATORENAL VASOTROPIC FACTORS

In connection with the discussion of shock it is valuable to note recent studies of vasotropic factors formed in the kidneys and liver during hypoxia. In studies of the mechanism of shock, Chambers, Zweifach, Lowenstein, and Lee[343] showed that humoral agents play an important role both in the early vasoconstriction which attends all forms of circulatory failure, and in the vasodepression which characterizes shock in its terminal and irreversible state. Knowledge of these humoral agents, known as VEM (vasoexcitor material) and VDM (vasodepressor material *or ferritin), comes primarily from observations on the spontaneous* activity of the terminal muscular vessels, the meta-arterioles and precapillaries, and on their threshold of reaction to adrenalin. The organ chiefly used in these studies is the exteriorized mesoappendix of the anesthetized rat. The observations of these investigators, and the subsequent studies of Shorr, Zweifach, Furchgott, and Baez,[1881, 1885, 1886, 1888] have shown that VEM is formed in the renal cortex, while VDM is formed in the liver and to a lesser extent in the spleen and skeletal muscles. The formation of both VEM and VDM *in vitro* is limited to states of reduced oxygen tension; under aerobic conditions, VEM is inactivated by the normal kidney and VDM is inactivated by the normal liver. The formation of VEM, which predominates in the peripheral plasma *during the hyper-reactive phase of shock, is presumably* initiated by a reduction in oxygen tension in the kidneys during severe renal ischemia and perhaps under other circumstances. The formation of VDM, which predominates in the peripheral plasma during the late hyporeactive (irreversible) stage of shock, is *presumably* initiated by a reduction in oxygen tension in the liver during severe

hepatic ischemia, and perhaps under other circumstances. Both phenomenon represent reactions of the Pasteur type analogous to the formation of lactic acid by normal tissue under anaerobiasis and its destruction by oxidation under aerobic conditions. But in the terminal and irreversible phase of shock, the hepatic mechanism for inactivating VDM undergoes deterioration, and hence VDM comes to predominate in the systemic circulation. It is be-

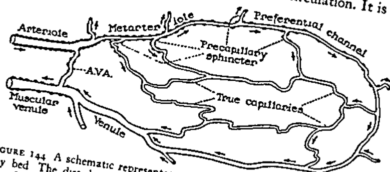


FIGURE 144 A schematic representation of the structural pattern of the capillary bed The distribution of smooth muscle is indicated in the vessel wall. (Zweifach [illegible])

lieved that it is this circumstance which accounts for the irreversibility of this terminal phase.

When injected into the test animal, VEM increases the spontaneous vasomotion of the meta-arterioles and precapillaries, thus confining the blood more or less to the so-called 'thoroughfare' vessels which communicate directly between the meta-arterioles and the venules, with minimal circulation through the true capillaries (fig. 144) VDM, on the other hand, decreases the vasomotion of the meta-arterioles and precapillaries and dilates the precapillary sphincters, thus permitting the blood to flow widely into the capillary plexus at a relatively high pressure.

Until recently much of the study of these agents has been concerned with shock, but the appearance of one or the other of them in the blood in other circumstances (essential hypertension, ch. XXIII; cardiac failure, ch. XXII; nephrosis, ch. XXVI) enhances heir interest to the renal physiologist. The interpretation developed in relation to shock is that the initial reaction to blood

loss involves a reduction in renal blood flow sufficient to initiate the anaerobic process in the kidney, which leads to the formation of VEM. This agent, by *augmenting the constrictor* phase of vasomotion in the meta-arterioles and precapillaries, diverts the blood through the 'thoroughfare' vessels and restricts the blood flow through the capillary bed in a manner which sustains the effective circulating blood volume. Thus, the passage of VEM into the blood stream leads to the development of a type of vascular hyper-reactivity favorable to the maintenance of an adequate circulation in the face of reduced blood volume. During this phase, recovery can be effected by transfusion. If, however, the shock is prolonged and hypotension profound, the renal blood flow is virtually abolished and there is no further release of VEM into the blood stream. The reduction in blood flow to the liver is now sufficient to initiate the anaerobic process which leads to the formation of VDM, and this agent eventually appears in the blood in sufficient amounts to dominate the terminal vascular bed. The effect of VDM is to depress vasomotion in the meta-arterioles and precapillaries and to dilate the precapillary sphincters, thus permitting blood to pass in excessive amounts into the capillary bed with the production of capillary congestion and irreversible reduction in effective circulating blood volume. In this phase the animal cannot be saved by transfusion. It is perhaps significant that Frank, Seligman, and Fine [685] find that the maintenance of an adequate blood flow through the liver while the remainder of the organism is subjected to the deficient blood flow of prolonged hemorrhagic shock protects it from developing 'irreversibility' (a circumstance which may be related to VDM). This observation has been confirmed by Cohn and Parsons.[394]

Under the dominance of VEM, blood is diverted from the capillaries through the 'thoroughfare' vessels and capillary pressure is reduced, with the result that extracellular fluid moves back into the capillaries, leading to hemodilution (characteristic of the early phase of shock). Under dominance by VDM, the meta-arterioles and precapillary sphincters are dilated and capillary pressure is increased, leading to excessive filtration of fluid and hemoconcentration (characteristic of terminal stages of shock).

VDM has been identified as ferritin, the protein moiety being

the effective agent.[1426] VDM is antidiuretic and apparently act through the neurohypophysis (Shorr, pers. com.).

THE ROLE OF HEMATOGENOUS CASTS IN RENAL FAILURE AND THE CONDITIONS OF THEIR FORMATION

The Hematurias

In renal failure associated with the excretion of blood pigments, hematogenous casts are rarely found in the proximal tubule or thin segment, * they first appear in the ascending limb of the distal tubule and increase in density in the distal convoluted tubule and in the collecting ducts. In the presence of proteinuria, casts of albumin and globulin may form in these same segments. Whether the appearance of casts in the collecting tubules implies further reabsorption of water there or merely delay in precipitation after concentration in the distal convoluted tubule or, alternatively, dislodgment from the distal segment, is not known. Casts may be present without evidence that they obstruct the flow of urine, but most investigators accept their presence as presumptive evidence both of obstruction and of local injury of the tubule wall.

Hemoglobin is the characteristic urinary pigment in transfusion reactions, though some methemoglobin is generally present, and hemoglobinuria [1745] may accompany any circumstance in which intravascular hemolysis occurs Sulfanilamide and other sulfa drugs cause hemolysis in some sensitive individuals, as may quinine in massive doses, the bites of certain snakes and spiders, the toxin of Clostridium welchii and arsine. In blackwater fever, where intravascular hemolysis is associated with malarial infestation, the urinary pigment is chiefly methemoglobin. Favism is a form of acute hemolytic anemia with hemoglobinuria, which is caused in sensitized persons by the ingestion of the green seeds of the fava bean or by the inhalation of its pollen It occurs most frequently on the island of Sardinia, and is fairly common in Sicily and in some districts in Italy. A genetic factor apparently underlies sensitization Oliguria, renal failure, and death in uremia occasionally follow the hemoglobinuria in severer attacks.

* An exception to this statement is Bence-Jones protein, commonly associated with multiple myeloma, which also precipitates in the proximal tubule.[1110]

Intravascular hemolysis is now recognized as playing a role in renal failure associated with irrigation of the bladder with distilled water during transurethral resection of the prostate.[451, 452, 1209, 1346, 2272]

Paroxysmal nocturnal hemoglobinuria is characterized by hemolytic anemia, with bouts of hemoglobinuria occurring mainly while the subject sleeps. The primary abnormality lies in the red cells which are lysed by a thermolabile fraction of normal serum. No cure for the disease is known, and the course is irregularly downhill over a period of 7 to 10 years, with death usually from intercurrent infection.[1388]

Paroxysmal cold hemoglobinuria involves a unique hemolysin, is associated with reduction of the surface temperature of the body, and in most instances is of short duration. A typical attack may be induced by immersing the arms and legs in ice water for a few minutes (a procedure which in some patients may be dangerous). Vasomotor disturbances of the Raynaud type are often present. In one type there is either clinical or serological evidence [illegible]

ical trauma and is generally characterized by *in vitro* agglutination of the red cells on reduction of temperature (cold agglutination).[1371]

Hemoglobinuria may also be associated, if infrequently, with postural proteinuria.[2252]

Myohemoglobinuria is an extremely rare disease in man;[323] it occurs frequently in work horses (paralytic myohemoglobinuria) and renal failure and uremia may prove fatal.[1169] *Haff* disease is a similar condition in man caused by eating fish or eels poisoned with resinous acid wastes from the cellulose factories near Königsberg. It is characterized by paroxysmal attacks of pain, stiffness and limitation of motion of striated muscles, and *myohemoglobinuria*.[1745]

According to Oliver,[1860] protein-containing urine is a system in which stability is determined by equilibria involving (a) the concentration of electrolytes and urea, (b) the concentration and nature of the protein, (c) the pH, and (d) the concentration of a

non-dialyzable heat-resistant body (x-body), which may be chondroitin sulphuric acid (see also Melohn *et al.*[1480]). Increasing concentrations of electrolytes and urea and of the protein tend to maintain stability; increasing concentrations of H ions and of the x-body tend to promote coagulation. The behavior of protein systems toward the metachromatic reaction (familiar to pathologists as a shift in color with certain dyes, as for example toluidin blue) is analogous to their behavior in regard to coagulation. Orthochromasia is the analog of dispersion, and metachromasia of coagulation. The coagula formed from protein and *x*-body are strongly metachromatic; coagula formed by heat and salts are orthochromatic.

Human hemoglobin does not agglutinate cells of the four main blood groups. There is, however, a strong pressor factor in uncrystallized hemoglobin solutions.[49] In some instances where adverse reactions have followed the administration of pigments, one may suspect the presence of pyrogens which will induce nausea, chills, fever, back pain, and, more importantly, if the pyrogenic reaction is a severe one, hypotension and transient renal failure.

It has been adequately demonstrated that purified, cell-free homologous pigments can be administered in large quantities to normal animals and man [2255] without producing any renal injury. In addition to the studies cited in chapter VIII, it may be noted that de Navasquéz [607] observed that massive hemoglobinuria, even with an acid urine, might be non-injurious in man, and he failed to produce renal injury by the injection of large doses of this pigment into normal rabbits. Myohemoglobin [423] and methemoglobin [172] are not injurious to normal dogs, and myohemoglobin [319] and hemoglobin [72 607 2287] are not injurious to normal rabbits. From the early work of Mason and Mann [1414] and Reid,[1691] it has been believed that the debris of laked cells induces severe vasomotor reactions and oliguria, but this view has recently been challenged by Maluf [1378] (*vide infra*)

Cannan and Redish [326] prepared pure hemoglobin by crystallization and administered it in man in single doses up to 0.64 gm/kg with no evidence of adverse renal effects. Amberson, Jennings, and Rhode [49] studied the effects of hemoglobin-saline solution as a blood substitute and administered it in total quantities up to

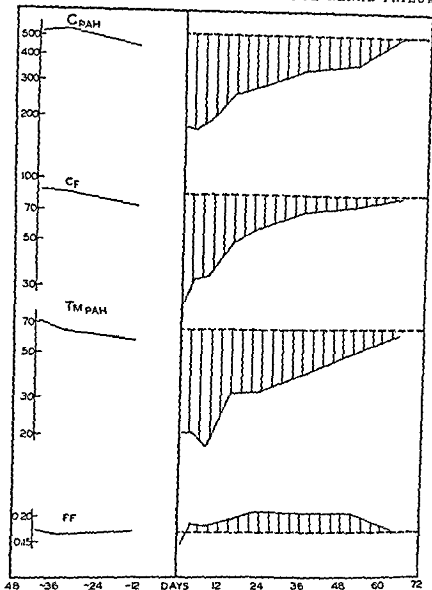


FIGURE 145. An anomalous reaction to hemoglobin. The patient was a 60-year-old woman suffering from rheumatic arthritis and hypertension. After 3 control studies she was given 200 cc. of hemoglobin-saline solution (24 gm. hemoglobin) intravenously. There was no obvious adverse reaction, yet severe renal impairment resulted Recovery to original function occurred only after 2 months. At no time was oliguria present. In view of the general absence of injurious effects from the injection of hemoglobin in man and dogs, this reaction must be considered unusual. (Amberson, Jennings, and Rhode [19])

nearly 80 gm. Such solutions were infused 77 times, and 7 cases received from 3 to 18 infusions. Only twice (once in a case of shock and once following the injection of a pyrogenic solution) did oliguria occur. In 1 subject, 4 determinations of the PAH clearance before infusion gave 1054, 993, 1208, and 955 cc. On the day after infusion, values of 1222 and 1030 cc. were obtained. A second subject with rheumatoid arthritis and hypertension was studied in greater detail and showed adverse renal effects (fig. 145). In 3 sets of observations before infusion, the mannitol clearance averaged 86 8, 84.9, 72 6, the renal plasma flow 511, 523, 429 cc., and Tm_D 71.2, 63.6, 56.9 mg of iodine Twenty-four hours after a single infusion of 200 cc. of non-pyrogenic hemoglobin-saline solution, these values fell to 24 9, 194, and 20, respectively. Intermittent studies revealed that renal function recovered to normal levels, but 2 months were required for it to do so Amberson and his coworkers note that this severe and persistent impairment of renal function would not have been disclosed by observations on the nitrogenous elements of the blood alone. It is particularly noteworthy that the urine volume was well maintained throughout, rising somewhat in the first day and continuing thereafter within normal limits. It is impossible to say what happened to bring about an adverse reaction in this patient It certainly cannot be attributed to hemoglobin *per se*, it possibly involved a vascular reaction with renal ischemia and reduction of filtration rate such as appears to be necessary for the production of protein casts, with hyposthenuria in the residual functional tissue.

Numerous investigations have been carried out (mostly on the rabbit, unfortunately) of the circumstances predisposing to obstructive cast formation, generally under the unwarranted assumption that cast formation is a necessary condition for the production of oliguria. These investigations may now be reviewed in the light of what is known about the reaction of the renal circulation to circulatory and other disturbances.

Baker and Dodds,[74] from experiments with rabbits (which are highly sensitive to psychogenic renal vasoconstriction), concluded that hemoglobin and its derivatives, particularly methemoglobin and hematin, precipitated and blocked the renal tubules when the urine was acid (ammonium chloride acidosis), and they advocated

the administration of alkali to prevent this precipitation. The importance of an acid urine has not generally been confirmed. De Gowin and his coworkers,[495,496] using dogs, believed that mechanical obstruction of the renal tubules could not explain all their deaths, and they inferred the presence of a nephrotoxic factor causing necrosis of the tubular epithelium. Neither group of investigators adequately controlled the state of hydration of their animals or measured the filtration rate.

Yuile, Gold, and Hinds[2287] found that to produce hemoglobin casts in rabbits it was necessary not only to have the urine acid but also to induce a short period of renal ischemia or to administer sodium tartrate, which is known to injure the tubules. Foy, Altmann, Barnes, and Kondi[685] suggested that ammonium chloride itself might be responsible for the renal lesion, a point supported by Govan and Parkes.[881] But Badenoch and Darmady[72] found that mechanical reduction of the renal circulation for a period of 90 min., coupled with the injection of stroma-free hemoglobin, led to a higher percentage of deaths in rabbits than either procedure alone.

Bywaters and Stead[319] were unable to reproduce the renal effects of the crush syndrome using rabbits whose muscles are virtually devoid of myohemoglobin. The injection of myohemoglobin into normal rabbits was without effect, but fatal uremia was precipitated in 4 out of 25 aciduric rabbits, with varying degrees of azotemia in 15 others. Again neither dehydration nor the toxic effects of large doses of ammonium chloride were controlled. Renal injury was obtained by Bywaters and Stead[319] when myohemoglobin was injected into rabbits after release of a standardized leg compression, and Corcoran and Page,[423] although failing to obtain renal injury of uremic degree with myohemoglobin in normally hydrated aciduric rats, succeeded in doing so in dehydrated rats whose legs had been crushed.

It seems probable that, in all the positive experiments reported above, a critical reduction in filtration rate or urine delivery to the distal system had been induced by the experimental procedure (dehydration during ammonium chloride acidosis, mechanical reduction of the renal circulation, sodium tartrate intoxication) and that cast formation is attributable to the excretion of pigment

under conditions where the tubular reabsorption of sodium and water is very great. Yorke and Nauss [2281] long ago emphasized that hemoglobinuric 'nephrosis' was most consistently obtained in rabbits during a period of hypotension, pointing, in the light of the present evidence, to the possible importance of reduced filtration rate. More recently Lalich [1189,1190,1193] has shown that dehydration and reduction of body fluids in this species predisposes to acute renal injury. He believes, however, that an acid urine *per se* possibly promotes cast formation. Lalich [1191] has also shown that rabbits in which extensive tubular casts have been produced by a combination of dehydration and hemoglobin injection can, if they survive the acute phase of renal failure, withstand uninephrectomy. Examination of such excised kidneys reveals that pigment casts, tubular dilatation, and vacuolization of the epithelium require 34 to 116 days for their resolution.

Bing [173] obtained severe renal injury in unanesthetized dogs by the intravenous injection of crystalline methemoglobin (3 to 13.5 gm) if the animals were first rendered acidotic with ammonium chloride (blood pH 6.9 to 7.2), but again dehydration was not controlled. Immediately after the beginning of the injection the creatinine and PAH clearances began to decrease in a parallel manner, falling to 10 per cent of the control value within an hour or so, and on the third day the animal was severely oliguric and diuresis could not be established with mannitol. But despite this sharp drop in renal function, pigmented casts were never found in the urine Most animals were moribund on the third day and had to be sacrificed, but one survived 13 days during which time the blood urea rose from 16 to 170 mg. per cent. Tm_{G} was sharply decreased with other renal functions. Histological examination of these kidneys revealed normal glomeruli; the proximal tubules showed hydropic degeneration and the distal tubules patchy areas of necrosis. The collecting ducts were plugged with protein material but not dilated, and some were calcified. Pigmented casts were observed in the tubules of only 2 kidneys, from animals that had received 3 infusions of methemoglobin on successive days It may be noted, however, that in Bing's positive results with methemoglobin in dogs, marked renal ischemia and reduction of filtration rate were present before the end of the injection or

shortly thereafter. The cause of this renal shut-down is not known, but Bing's inference that cast formation is probably a sequel to a reduced filtration rate may be affirmed. The fact that an acid urine promotes the precipitation of methemoglobin appears to be a secondary matter. Infusion of methemoglobin into normal (non-acidotic) dogs had no adverse effects upon renal function but in general caused an increase in creatinine and PAH clearances. Depression of renal function was never observed and histologically the kidneys showed no injury.

Crystalline hemoglobin (4 to 10 gm.) and myohemoglobin (4.7 to 7.3 gm.) produced only a slight, transient decrease in clearances in both normal and acidotic dogs, with no pathologic changes in the kidneys and no cast production. Control studies showed that severe acidosis induced by the injection of lactic acid or hydrochloric acid, or the oral administration of ammonium chloride, had no lasting effects on filtration rate or renal blood flow or on the structure of the kidney. The first two produced a transient drop in clearances which Bing believed was related to the formation of methemoglobin at the point of mixing of the strong acid solution with the blood stream.

Corcoran and Page [422] studied the effects of myohemoglobin (beef heart) given intravenously to dogs in which the urine had been acidified by a high protein diet and the daily administration of sodium dihydrogen phosphate. In 5 out of 10 experiments the diodrast clearance increased slightly, but in the average there was a slight (5 per cent) decrease; the inulin clearance, however, decreased by nearly 30 per cent and Tm_D decreased by 50 per cent. Two or 3 days after injection the diodrast clearance was reduced while the inulin clearance and Tm_D had improved but were still below the control values. Some 2 weeks after injection these functions became stabilized at slightly sub-control levels. In some experiments Tm_D was less 48 hr. after injection than it had been at a time when myohemoglobinuria had substantially ceased. The degree of renal injury, as judged by the reduction in Tm_D, roughly increased with the quantity of myohemoglobin retained in the body. Myohemoglobin and metamyohemoglobin could not be distinguished by their effects. There were no deaths in uremia.

Hematin (23.7 mg/kg.), which proved to be quite toxic, caused

an immediate decrease in diodrast clearance and Tm_D, the inulin clearance being unaffected at first; later this clearance decreased with further decreases in diodrast clearance, Tm_D recovering slowly. A larger dose (32.6 mg/kg.) of hematin caused both inulin and diodrast clearances to fall to very low levels with ensuing oliguria, associated with shock and fatal termination, in 12 hr. The dosage of hematin appears to be critically narrow.

Corcoran and Page suggest that the sequence of events is (1) filtration of pigment, (2) athrocytosis by the tubules and (3) conversion to methemoglobin or metamyohemoglobin in the acid urine of the distal tubule, and (4) degradation to hematin which, being difficultly soluble, is deposited and forms the nucleus for cast formation. Since Tm_D is more markedly affected than the renal plasma flow, with intermediate effects on the filtration rate, they favor the theory that obstructive cast formation is primary and is accompanied by some renal hyperemia (vicarious clearance) of residual functional tissue. They believe that their observations show that renal ischemia is not present and plays no role in renal injury.* In so far as Tm_D and the filtration rate are depressed proportionally, they assume that the change in both is the result of tubular obstruction. They give reasons for believing that the reduction of Tm_D beyond the degree of glomerular reduction is due to injury of the proximal tubules by athrocytosis of the pigment.

Corcoran and Page record data on 3 aciduric dogs injected with hemoglobin. In only 1 dog was renal function significantly impaired, the filtration rate decreasing to the range of 32 to 60 per cent of normal, which might have led to slight azotemia. They state that the renal effects of hemoglobin are similar to those of myohemoglobin, but only in 1 dog did Tm_D decrease markedly. Their inference that the difference in effects is attributable to differences in the molecular weight of the two pigments is plausible, but Bing obtained complete renal failure with azotemia and cast formation in the collecting tubules with methemoglobin, which has the same molecular weight as hemoglobin.

Corcoran and Page report no data on NPN, but one surmises

* This may be true under the conditions of their experiments, but it is not applicable to circumstances where renal ischemia is known to be present

that, among their aciduric dogs injected with metamyohemoglobin and myohemoglobin, only 1 (no. 15-62) out of 11 would have developed detectable elevation of NPN, the decrease in filtration rate rarely exceeding 20 per cent at any time. In only 1 of 3 dogs receiving hemoglobin was the filtration rate reduced significantly. The combination of myohemoglobin and acidosis did not produce renal failure in dogs, and one infers that it would have to be supplemented by renal ischemia.

Flink [663] injected massive doses (4 to 6 gm/kg.) of hemoglobin into dogs and found just as severe renal damage during alkalinuria as during aciduria. He found no difference between the effects of solutions of hemoglobin crystals and of lysed red cells. When the initial concentration of hemoglobin in the plasma exceeded 3.7 gm/100 cc., or the average of 2 concentrations was over 2.2 gm/100 cc., *renal insufficiency always developed. But below these levels all dogs recovered without any signs of renal damage.* Renal damage was manifested by azotemia, albuminuria, cast formation, and the excretion of relatively large volumes of dilute urine. *Anuria did not occur, although hemoglobin casts were found in the majority of tubules.* Flink's results suggest obstruction of many nephrons with hyposthenuria in the residual functional tissue. However, it must be noted that to secure renal injury he had to obtain plasma concentrations of hemoglobin far higher than have been used by other investigators or than ever occur in man.

Harrison, Bunting, Ordway, and Albrink [670] obtained *oliguria in dogs* following intravascular hemolysis produced by arsine and by the injection of massive doses of hemoglobin and methemoglobin *in sufficient amounts to give plasma concentrations of 1 gm/100 cc.* or more. Immediately after the injection the endogenous creatinine clearance fell to low figures, but they *failed to obtain evidence of a reduction in renal blood flow* by a cannulation method. (This is evidence of obstruction of the tubules.) Methemoglobin proved to be more toxic than oxyhemoglobin. The authors conclude that tubular obstruction is an important factor in the early reduction of kidney function, the obstructing casts being chiefly methemoglobin in concentrated solution *of a gel-like consistency.* No evidence of formation of a pigment insoluble at the pH of the urine, such as hemochromogen or hematin,

was found. They believed that cessation of urine flow is attributable to the increased viscosity of the tubular contents. Necrosis of the proximal tubule was present as a late lesion, and they conceive that this injury is probably a contributing factor in the persistent severe depression of renal function. By means of the ferrocyanide histochemical method, it was demonstrated that filtrate continued to be formed in obstructed nephrons, although there was no evidence that the tubules were sufficiently injured at this stage to permit extensive báck diffusion, the ferrocyanide failing to penetrate the tubule cells as it does in mercuric chloride poisoning.

Maluf [1376] reports that lysed red cells, equivalent in quantity to a liter of blood in a 70 kg. man, may be injected intravenously into normal, well-hydrated dogs without producing any sign of renal damage, even with an initial urinary pH of 5.5 to 6.0. Thus the role of stroma and cell fragments is de-emphasized. If, however, the dog is dehydrated until its urine flow is only 0.006 cc/min. per kg., Maluf finds that half this quantity of lysed cells leads immediately to anuria or oliguria and uremia. Where normally during oliguria the urine is concentrated, in this post-infusion reaction the urine becomes very dilute, indicating either a marked shift in glomerular-tubular balance or rapid impairment of concentrating power in the distal system.

Maluf finds that in hydrated dogs lysed cells have no effect, as observed 24 hr. later, on the filtration rate, PAH clearance, or Tm_{PAH}. However, in dehydrated dogs, in which the filtration rate and PAH clearances are somewhat reduced initially, the cells precipitate a post-infusion reaction in which these functions are reduced to 1 per cent or less of normal. Comparable amounts of lysed cells also produced renal failure and anuria with uremia in dogs which were in reversible histamine shock at the time of infusion. Renal denervation prior to infusion did not prevent this renal failure, and there was no evidence of renal edema. When frozen sections were made of formalin-fixed material, many tubules in a field were found to be occluded by brown casts or crystals. However, he found no evidence, by the injection of India ink, of a decrease in absolute renal blood flow in the anuric kidney or of diversion of blood from cortex to medulla; and he concludes that

renal failure under the conditions of his experiments is attributable to tubular obstruction by hemochromogen casts, cast formation requiring a reduced filtration rate. He notes that patients to whom transfusions of blood are given are usually hypovolemic and suffering some degree of shock, and that one may assume the existence of renal ischemia and reduction in filtration rate.

CRUSH SYNDROME

Bywaters and other British pathologists[108,114,115,116,117] drew attention early in World War II to renal lesions in persons dying of anuria following crushing injury to skeletal muscle. The 'crush syndrome' is characterized by shock, azotemia, hypotension, and uremia, death in anuria ensuing up to 20 days after injury. The renal pathological picture has been called 'lower nephron nephrosis' by Lucké,[1277] who stated that it was the most frequent form of fatal renal disorder encountered among military personnel during World War II and that it was present in 10 to 20 per cent of deaths resulting from all battle wounds. He further suggested that 'lower nephron nephrosis' was a common end reached in many of the clinical disturbances listed at the head of this chapter as leading, directly or indirectly, to anuria. He applied the terms 'lower nephron nephrosis' because from his own pathological material and descriptions of others he believed that the distal tubule only was affected. This conclusion appears to be inaccurate, however (*vide infra*). It was Lucké's opinion that the lesions result from several factors acting in combination: degradation products of hemoglobin or myohemoglobin, tissue breakdown products, alteration of blood and body fluids, and shock and other disturbances which lead to renal ischemia and anuria.

In the light of the observations cited above on the renal blood flow in shock, Lucké's emphasis on the role of renal ischemia in the genesis of renal injury is probably warranted in many instances. However, the specific or quantitative role of renal ischemia remains to be defined. In summarizing the literature on clinical anuria up to 1947, Corcoran and Page[420,421,424] divided post-traumatic anurias into two groups, those in which the primary lesion is obstruction of the renal tubules by hematogenous casts, and those in which the injury consists principally of necrosis of the

tubules. They expressed the opinion that the underlying mechanism in both types is renal ischemia which results in oliguria, and that this condition, associated with aciduria, predisposes to precipitation of protein in the renal tubules. They noted that myohemoglobinuria and hemoglobinuria, which cause little injury under normal conditions, resulted in severe renal injury only in the presence of renal ischemia. Thus considered, renal ischemia is important in the sequence of events leading to anuria, even where obstructive casts presumably are present.

Bywaters and Dible [216,217] and Mallory [1372] believe that all cases of true 'lower nephron nephrosis' are associated with muscle injury or intravascular hemolysis, and that the precipitation of pigment in the distal tubule and collecting ducts, though perhaps not the only factor, is a highly important one in causing anuria.

On the other hand, Foy, Altmann, Barnes, and Kondi,[655] Darmady,[467] Penner and Bernheim,[1686] and Snyder and Culbertson [1958] lean heavily toward renal ischemia as an important, if not primary, factor. The last-named investigators state that shock was present in 94 out of 99 cases reported by them, and that the 5 cases without shock were complicated by sulfonamide, crush injury, or transfusion reaction. However, they also emphasize the almost invariable presence of pigmented casts in necropsy specimens Maegraith, Havard, and Parsons,[1366] confirmed in the belief that renal ischemia is primary, forthrightly called the syndrome 'renal anoxia.'

Alternatively, Peters [1800] believes that increased renal interstitial pressure is the sole cause of oliguria in the crush syndrome, an interpretation refuted by Bywaters and Dible's [217] observation that there is no significant renal edema in human crush syndrome victims when survival is under 5 days. When present, the edema may be the result of the over-enthusiastic administration of saline, and consequently is most likely to make its appearance late in the oliguric period.

Any opinion in this question is probably immature. The problem of cast formation is obviously a complicated one. The evidence indicates that all the pigments tried (with the exception of hematin) are innocuous in normal animals in respect to both the

systemic circulation and the kidneys. Acidification of the urine is not sufficient to cause protein precipitation invariably, and when it does one may suspect the presence of one or more additional factors Casts have been produced experimentally most consistently in rabbits, in which the sympathetic system is highly labile [285] and in which acidotic diets, dehydration, or other circumstances may have reduced the filtration rate; in rabbits and rats whose legs have been crushed; and in dogs under conditions which reduce the filtration rate and upset glomerular-tubular balance.

It is important that, in our present view, a marked reduction in the filtration rate, however caused, will establish conditions favorable to increased sodium and water reabsorption in the proximal system. The distal load of sodium and water is thereby markedly reduced, water diuresis is blunted or absent, and the patient *enters into a refractory oliguria. Under these conditions and before* anoxic injury of the distal tubule occurs, the complete or almost complete reabsorption of sodium and water distally may lead to a maximally concentrated urine, favoring the precipitation of whatever proteins may be present in the distal segment and collecting tubules. It is consonant with this view that acute renal failure is so *frequently preceded by a recognizable or presumptive physiological* debacle which involves circulatory insufficiency (frank shock need not be present) and/or increased sympathetic activity and/or allergic reactions (for which there is no functional evidence at present) which may reduce the filtration rate. Severe oliguria, issuing from the excessive reabsorption of sodium and water, may be anticipated whenever the filtration rate in a subject with otherwise normal kidneys is reduced to or below 70 cc/min. per 1.73 sq. m.—the figure is necessarily an approximate one.

This tentative assessment of the importance of reduced filtration rate in cast formation does not exclude independent tubular injury due to chemical poisons (carbon tetrachloride), the excessive athrocytosis of hematogenous pigments (as suggested by the reduction of Tm_D reported by Corcoran and Page after the injection of myohemoglobin and metamyohemoglobin), or the toxic (vascular and tubular?) effects of hematin. When we supplement this interpretation with the fact that, as Harrison *et al.*[920] point out, colloidal pigments may obstruct urine flow simply by their

viscosity and without the formation of solid casts (although such soluble material may be overlooked in conventional methods of tissue fixation), the contradictions among various investigators do not appear to be insurmountable

We cannot, however, assert that the sequence of events in obstructive anuria is to be wholly described by cast formation.* The evidence is clear that protracted anoxia of the renal parenchyma, without any apparent possibility of cast formation, can lead to irreversible tubular injury. If the evidence on experimental animals can be transferred to man, it indicates that, during clinically induced ischemia, irreversible renal injury may be effected by complete cessation of renal blood flow in something between 3 and 4 hr., and probably within 6 hr If the ischemia is incomplete, a mere trickle of blood, representing no more than 5 per cent of the normal circulation, may suffice to maintain vitality in large areas of the renal parenchyma, and the critical period may be longer, though how much longer no one knows But other insults, such as chemical intoxication, allergy, etc., may substantially shorten it. It must not be overlooked that such deleterious factors may be present in crush injury, burns, and intestinal obstruction Renal ischemia of some degree accompanies all conditions of circulatory failure (shock, burns, etc.) and may accompany many other severe systemic reactions (infections, sulfa drugs, etc), but the problem remains to determine the degree of this ischemia and extent of injury which it can inflict on the kidneys when it is clinically induced. Secondarily, this exploration must be supplemented by an earlier and more rigorous search for evidence of intravascular hemolysis and pigment excretion.

Azotemia is generally attributable to decreased nitrogen clearance, chiefly urea, whether this decrease issues primarily from decreased filtration, increased back diffusion, or tubular obstruction.

* Oliver[1350] remarks, 'Perhaps in part because of its lack of imaginative appeal, most clinical students have shied away from the obvious conclusion that [illegible]

analysis, water cannot flow through stopped pipes'

Since the reabsorption of urea normally increases markedly at very low urine flows, oliguria *per se* will promote the accumulation of urea, and antecedent oliguria of several days' duration should be carefully considered whenever there has been even moderate vomiting or diarrhea. If hematemesis is present, azotemia may result from increased protein metabolism even in the absence of reduced renal function,[2004] and increased protein metabolism may be contributory in other conditions.[192]

PATHOLOGY OF THE ANURIC KIDNEY

Gross Pathology

It is probable that there is no characteristic change in the gross appearance of the anuric kidney.[469, 1272] Many observers describe an enlarged, swollen, pale, or mottled kidney; the capsule is smooth and strips with ease, and on section the cortex may be somewhat widened and everted, oozing clear or slightly bloody fluid, especially after 5 days or more of anuria. In contrast to the pale cortex, the medulla may be purplish and dusky, with prominent striations. Lucké [1277] and Bywaters and Dible [317] mention a distinct white stripe in the inner zone of the cortex in some cases. To what extent these changes have any pathogenic significance is questionable, since the great bulk of reported cases were examined after 4 or more days of survival and following various therapeutic procedures, many of which included over-hydration and saline infusions, which alone may account for the renal edema.

Microscopic Pathology

The pathological picture associated with crush injuries and other forms of acute renal failure was not studied extensively before World War II, although several descriptions existed in the German literature. Attention was drawn to the clinical and microscopic features of the crush syndrome during the early years of the war by Bywaters and Beall [316] and others.[108, 1421] In 1946, Lucké reviewed 538 fatal cases associated with renal failure ensuing from various injuries (battle wounds, crush injuries, heat stroke, falciparum malaria, blood transfusion reaction, poisoning, etc.) [1277] and first used the terms 'lower nephron nephrosis' because of his

impression that the degenerative and necrotic changes were localized in the distal tubule.

The microscopic picture, as described by Lucké and most observers, is as follows.

Glomeruli

There is a general agreement that the glomerular tufts are normal in appearance. Their vascularity, however, is sometimes diminished. The capsular spaces are nearly always filled with a faintly eosinophilic, granular substance and are rarely dilated. Whether this material consists of lysed epithelial cells or protein is not clear; its presence is interpreted by some [417, 1277] as indicating increased permeability of the glomerular capillaries. At times there appears to be cuboidal swelling of the normally flat parietal epithelium of the capsule, most marked near the mouth of the tubule.

Proximal Tubule

The changes in the cells lining the proximal tubules are variously described as cloudy swelling,[1277 1278] early degenerative changes, or intense catarrh.[417] Actual necrosis of these cells is rarely described In comparison with other parts of the nephron the proximal changes are considered minimal. Many of the lumina contain an amorphous precipitate similar to that in the capsular spaces, and some contain detritus and masses containing recognizable cell membranes. Pigment casts are very rare. It is impossible to ascertain from the literature a quantitative estimate of proximal tubular casts, i.e. whether they are present in all the tubules, the majority of tubules, or are present in scattered individual tubules.

Thin Segment

This segment is normal in appearance, although there may be 'mild catarrhal changes.' The eosinophilic precipitate seen in the proximal tubule is present also in the thin segment. No pigment casts are recorded.

Ascending Limb of Henle and Distal Tubule

It is because of the marked changes found in these segments that the term 'lower nephron nephrosis' has remained in vogue. Char-

acteristically, there are scattered, focal areas of patchy distribution showing varying stages of degeneration, necrosis, and regeneration of the tubular cells. Frank degeneration is seldom seen before the fourth day. From the fifth day onward the remnants of necrotic portions of tubules may undergo complete disintegration and disappear. Regeneration occurs by proliferation of epithelium that has escaped irreversible injury, new cells creeping beneath the dead lining, which becomes detached and is cast off into the lumen where it further disintegrates. Within less than 10 days most damaged areas are completely relined. Sometimes there is overgrowth and plication of the new epithelium, with a striking concertina-like appearance.

There may be some distention of the lumina, especially where they are adjacent to large veins. This bulging into the vein may lead to tubulovenous rupture, with non-obstructive venous thrombi at the site of rupture.[552] Rupture of the tubules also occurs into the interstitium, with surrounding inflammatory reaction. Tubulovenous and tubulointerstitial rupture are generally seen after the fourth day, and are most frequent in the boundary zone of the medulla, where the thick ascending limbs of Henle are in intimate relation with the *vasa recta*.

The interstitial tissue shows numerous small scattered foci of inflammation surrounding areas of degenerated and necrosed tubules and their protruded material. At first lymphocytes and histiocytes predominate, but at later stages fibroblasts make their appearance. When survival exceeds a week, the destroyed parenchyma may be replaced by scar tissue. Edema is inconstant and rarely severe.

Casts found in these segments are generally of two types: hyalin deposits, similar to those seen in the capsule and in the proximal tubule, and pigment casts. The thick ascending limb contains many hyalin casts, although mixed casts or pure pigment casts are not infrequent in this region. Pigment casts become more numerous in the distal convoluted tubules and collecting ducts. They are benzidine positive, but give a negative reaction for iron and are generally considered to be derivatives of myohemoglobin or hemoglobin. Pigment casts are rare before 2 to 3 days [1372] (which may reflect a slow process of solidification of a viscous gel). Both

hyalin and pigment casts tend to form around particulate matter, such as degenerated epithelial cells or crystals. They present every variety of form from ribbon-like strands to hollow cylinders; they may be granular or clear, but are generally smooth and solid in texture. Casts may be entirely absent from the distal tubule.[1277] Where survival exceeds 7 days, leukocytic infiltration of casts occurs, the pus-filled tubules almost resembling pyelonephritis,[317] although the inflammation is apparently aseptic.

Collecting Tubules

Pigment casts are most prominent here. The cellular changes are similar in nature to those in the distal tubule, but opinion differs on the extent of cellular damage. Lucké reports an almost normal appearance of the distal tubule cells, while others[317, 483] describe intense necrotic and regenerative changes.

It is possible that, in an effort to find a broad anatomic classification for lesions which appear similar clinically, there has been too much emphasis put on the 'lower nephron.' It is unfortunate that this term has for some writers come to signify a disease entity—there is no such disease as 'lower nephron nephrosis.' It would appear that, in animal kidneys subjected to clamping of the renal artery, the proximal tubule is the first to show injury,[1146, 1372, 1773, 1777, 1821] changes in the distal tubule occurring later and possibly to some extent as a result of cast formation which may itself issue from proximal injury. Human kidneys coming to necropsy are of course likely to reflect 4 days or more of anuria, when distal cast formation and damage therefrom have reached their peak.

From his study of teased, intact nephrons from humans dying in acute renal failure and dogs dying from hemorrhagic or traumatic shock, Oliver has been led to discard any specific localization, in the lower nephron or elsewhere (pers. com.). He reports scattered focal lesions, with destruction of the entire tubular wall including the basement membrane, throughout the entire length of the nephron and [illegible]

The kidney of acute renal failure does not represent a true nephrosis, such as occurs in mercury or uranium intoxication where

every nephron in both kidneys is similarly and equally affected with no destruction of the basement membrane, and it would seem appropriate to reserve the term nephrosis for such bilateral, uniformly dispersed injury.

On the basis of available evidence it would seem that the probable sequence of events in acute renal failure is as follows: widespread, scattered tubular damage (ischemic, allergic, nephrotoxic) affects any or all segments of the nephron; the accumulation of casts in the distal tubule and collecting ducts (the site of greatest concentration of the urine) exaggerates the injury to these segments, and leads to tubulovenous or tubulointerstitial rupture. Thus the lesions in the distal system are more evident and more frequently reported by most observers. No constant pathological picture has been observed, nor is it to be expected in a variety of circumstances where uncomplicated renal ischemia, renal edema, pigment casts, and nephrotoxins (carbon tetrachloride) contribute varying elements to the renal debacle. It would seem better to describe the lesions in such kidneys as they are observed, rather than to attempt to categorize them under a convenient and frequently misleading label.

TREATMENT OF ANURIA

The treatment of anuria should be conservative. If circulatory failure is present, appropriate steps should be taken to correct it. Otherwise therapy is limited to the balanced maintenance of the patient until the kidneys have a chance to effect recovery. According to the available evidence, if renal ischemia is complete, tubular injury from which the patient cannot quickly recover may be effected within the first few hours of the anuric period, and hence before the existence of anuria is recognized. Admittedly, it is possible that complete ischemia rarely occurs in man and that the critical period may be substantially longer, perhaps up to 24 hr. or more, but renal ischemia can persist for some hours after the restoration of blood pressure. In any case, it is likely that the damage has been done when the anuria is clinically discovered, and if so the only therapy available is to maintain the patient's well being by supportive and prophylactic measures through such time as is required for the kidneys to undergo reconstitution.

It is now widely recognized that a serious mistake of the past has been the zealous over-administration of fluid on the theory that the anuric patient was 'dehydrated,' but in simple dehydration uncomplicated by circulatory failure or renal injury, the kidneys excrete some 500 to 700 cc/day of a highly concentrated urine. *Oliguria or anuria implies a functional renal shutdown or severe* renal injury, and in the presence of either it is impossible to pump water or saline through the ischemic or blockaded organ by injecting fluid into the vascular bed. It is easy to expand the body fluids to such an extent as to produce dangerous pulmonary edema and perhaps to promote the formation of renal edema. Strauss [2019] notes that, before the use of parenteral fluids, completely anuric patients were reported as *surviving* 3 to 4 weeks, 1 for 5 weeks, 2 for 6 weeks, and 3 for 7 weeks, whereas more recent reports show a 50 per cent mortality within the first 6 days. He believes it highly unlikely that renal insufficiency *per se* in man would lead to death within such a brief period. The implication is that the administration of excessive parenteral fluid has increased short-period mortality by the production of pulmonary edema. Nothing in the experimental evidence indicates that renal denervation after anuria has developed would be of value, a conclusion supported by clinical experience. Decapsulation, despite some enthusiastic supporters,[3] is not recommended by others [480, 2014, 2103] and has been widely abandoned with the increasing recognition, first, that in many instances the renal edema which decapsulation is supposed to relieve is the result of over-administration of saline and, second, that spontaneous diuresis is likely to occur at just about the time when decapsulation is resorted to.* Although the artificial kidney, peritoneal dialysis, replacement transfusion, and intestinal irrigation are possibly useful in some instances in supporting the patient through a critical period of uremia, the indications for their use are not clearly defined. They cannot in themselves induce diuresis and their value in influencing the course of acute anuria, usually a self-limited disturbance, defies critical evaluation Since

each method involves an inherent physiological burden, the application of any of them may handicap rather than promote spontaneous recovery.[634, 659, 2014]

The most notable aspect of this problem is the remarkable capacity of the renal parenchyma to reconstitute itself after devastating injury. The clinical instances cited above show that, in patients in whom the total renal blood flow is but a few cc/min., the process of filtration is practically abolished, and the tubules are so severely injured as to have lost all excretory capacity, possibly to have lost their normal impermeability and even in many instances their physical continuity, the renal parenchyma slowly, over a period of 1 to 2 months, substantially reconstitutes itself and in a few more months returns to normal function, leaving in some instances no detectable deficit. But no measure is known that will restore a physiologically ruined kidney except time and the organ's intrinsic reconstitutive power.

Over the period of 7 days to 2 weeks in which this reconstitution must begin, the patient should be supported by the minimum of fluid required to offset insensible and uncontrollable water loss. The figure of 700 cc/day to cover insensible loss comes from data quoted by DuBois,[648] showing that in a large number of normal and diseased subjects observed at an average temperature of 22 to 25° C. and 30 to 50 per cent humidity, insensible water loss averaged 700 gm/day. In theory, one might deduct from this figure some 200 to 300 gm. for water of metabolism, but it is safer to leave a margin of safety. If fever, vomiting, diarrhea, or hot weather increases water loss, an equivalent amount must be added to the figure above.

Protein combustion should be kept at a minimum by the oral administration of sufficient fat and glucose to meet minimal caloric needs (1500 to 2000 calories/day) in order to reduce endogenous protein combustion, and acidosis, if present, should be corrected by the judicious intravenous administration of hypertonic (5 per cent) sodium bicarbonate, or the administration of this salt by mouth. (Lactate and citrate may be poorly oxidized in patients in shock, and indeed acidosis may be largely the result of failure to oxidize this and other acids) In general, it seems wiser to restrict sodium and fluids in the face of a mild to moderate

acidosis, the dangers of which are less than those of possible expansion of extracellular fluid volume and resultant pulmonary edema The urine in oliguria of renal failure is generally quite acid and cannot be made alkaline by the administration of bicarbonate, and therefore cannot be used as an index of acidosis On the other hand, excess alkali presents a real danger. Sodium should be restricted and potassium absolutely excluded, retention of the former leading to water retention when otherwise water might be excreted, and retention of the latter possibly leading to cardiac death[297,301,302,306,645,1175,1492,1493,1899,1857,1965,2014,2019,2092] Notable success has been achieved by Bull, Joekes, and Lowe[2916] in the treatment of patients with anuria of highly varied origin, utilizing an extremely conservative regime.

Burwell, Kinney, and Finch[305] point out that, whereas diuresis following anuria tends to occur between 7 and 10 days, with a mode at 9 and 10 days, there is also a second peak of deaths (in their limited data) on the tenth day. They associate these two facts in the belief that when urine flow is resumed the urine approximates the glomerular filtrate in composition, notably in respect to the fact that there may be an inordinate loss of (sodium) chloride, which may itself be deleterious. Thorn[2070] has reported hypochloremia during the initial diuretic phase, and pointed out that the administration of sodium chloride in large amounts at this time may be indicated to compensate for this excessive loss. Such therapy should, however, be utilized only in the face of demonstrated sodium loss; otherwise salt administration will invite pulmonary edema and contribute to delayed deaths.

CHAPTER XXV

The Juxtamedullary Circulation

In the discussion of the anatomy of the kidney (ch. 1) we have noted signal differences between the nephrons in the outer two-thirds of the cortex and those in the inner or juxtamedullary zone, particularly in respect to the fate of the postglomerular blood. To reiterate briefly, the efferent arteriole of a typical cortical glomerulus breaks up into a capillary plexus which enmeshes the adjacent proximal and distal tubules, while the efferent arteriole of a juxtamedullary glomerulus proceeds as a single large trunk into the medulla to form the *vasa recta* which loop back sharply and empty, like the cortical capillary plexus, into an interlobular or arcuate vein. The *vasa recta* are juxtaposed almost exclusively to the thin segments, which, with the collecting tubules, predominate in the medulla. The cardinal features of the cortical and juxtamedullary circulation are illustrated in plate 11 (ch. 1). In constructing this illustration we have followed closely the careful anatomical studies of Trueta, Barclay, Daniel, Franklin, and Prichard,[2083] which supplement the earlier descriptions of Peter [1595] and other anatomists.

Trueta and his colleagues find that under circumstances (tourniquet shock, etc.) inducing extreme vasoconstriction of the renal arterial tree the circulation in the rabbit may be largely or wholly diverted from the cortical to the juxtamedullary glomeruli. After

the application of a tourniquet to one of the hind legs of a rabbit for 4½ hr., the femoral and iliac arteries undergo marked constriction, the mesenteric arteries remaining unaffected. This arterial constriction is reflex in origin, and they report that it can be induced by stimulation of the central end of the cut sciatic nerve or the distal end of the divided splanchnic nerve and can be prevented by splanchnic section. Under these conditions the intensity of vasoconstriction varies radially through the kidney: the interlobular arteries and the cortical glomeruli are rendered ischemic while the juxtamedullary glomeruli remain under perfusion. India ink and other substances injected into the renal artery stain the juxtamedullary region and the medulla, but not the cortex.

More than local cortical ischemia is implied, for it appears that the juxtamedullary arterioles may themselves be dilated. The renal artery to renal vein circulation time of radio-opaque substances, as measured by rapid angiographic methods, is significantly reduced, and it is asserted that a stream of arterial blood may appear in the renal vein, or that the whole of the renal venous blood may become arterial in color,* and that the arterial pulse may be clearly visible in the vein, indicating that dilation within the juxtamedullary circuit is so great as to constitute a virtual arterial-venous by-pass.

This medullary diversion can be elicited by trauma and nerve stimulation, by severe, rapid hemorrhage, by the administration of adrenalin, pituitrin, and pitressin in large doses, and, in susceptible animals after a latent period of about 24 hr., by staphylococcus toxin. It is postulated that juxtamedullary diversion is a physiological mechanism involved in reflex anuria; the anuria associated with incompatible blood transfusions, crush injury, blackwater fever, etc.; the renal ischemia of tourniquet shock and the ischemia induced by fright or adrenalin; as well as in the antidiuretic action of pitressin and the genesis of essential hypertension.

* The renal oxygen arterial-venous difference in man is normally so small (0.7 to 2.0 cc/100 cc.) that the difference in color between arterial and renal venous blood is imperceptible and blood samples must be clearly marked in order to distinguish them

In some instances the vasomotor pattern may be reversed; i.e. in animals in which the splanchnic nerves have been divided prior to the application of the tourniquet, the vascular bed of the cortex may be dilated and that of the medulla constricted. Although diversion of the blood from the cortex to the medulla is the most frequent pattern, there is considerable variability of reaction, and indeed it is difficult to provoke complete reflex cortical ischemia consistently. Under apparently identical conditions the phenomenon may entirely fail to occur. These investigators believe that normally the greater part of the blood passes through the cortex and that significant diversion from cortex to medulla occurs infrequently in the quiescent state.

It should be emphasized that these workers by their careful injection methods failed to obtain evidence of arteriovenous anastomoses in the normal kidney of any species. They specifically deny Spanner's [1968] observations and state that he probably mistook certain coiled arterial twigs for such anastomoses. Direct arterioles to the tubules, such as *arteriae recta verae* and Isaacs-Ludwig arterioles, they attribute to degenerative canalization of glomeruli as a result of prolonged or repeated juxtamedullary diversion.

Trueta and his colleagues believe that the *vasa recta* present a capacious route by which blood may be diverted from the arterial to the venous side of the kidney during cortical ischemia without exposure to parenchyma other than the thin segment and collecting tubules that comprise the medulla.

An abundance of evidence is available which appears to refute this interpretation in man, and probably in the dog. Consideration of this evidence requires a brief restatement of the functions attributed to various segments of the nephron. On the positive evidence of Marshall,[1310] Chambers and Kempton,[342] Cameron and Chambers,[322] and Forster (pers. com.), the proximal segment, which appears to be homologous in all vertebrates, is the site of tubular excretion of phenol red and other substances that undergo tubular excretion, whereas the distal tubule, at least in tissue culture, is not involved in tubular excretion.[322, 342] By equation of their mutual interference in tubular transport, phenol red, diodrast, and PAH are excreted by the same cells and same segment.

No evidence can be adduced that the thin segment of the loop of Henle can excrete PAH or other substances. The cytological structure of the epithelium of this segment argues against such a view, and the presently accepted interpretation, based upon the evidence of electrolyte and water excretion, is that the thin segment is interposed between the proximal and distal tubules to promote the osmotic equilibration of the urine before the latter enters the distal system for the final and critical operations effected there (ch. XI).

OBSERVATIONS ON MAN

Normal Renal Circulation

It follows that for the complete clearance of PAH all the blood must in effect be presented to proximal tissue. Accepting, for the purposes of discussion, the functional interpretation placed upon the juxtamedullary circulation by the Oxford investigators, such blood as exclusively perfuses the juxtamedullary glomeruli and the *vasa recta* is not presented to proximal tissue and therefore must remain uncleared of PAH. In chapter VI we have cited the observations of numerous investigators which show that the extraction ratio of PAH (and diodrast) in the normal human kidney ranges from 0.88 to 1.00 and averages 0.91. Some of the renal arterial blood must perfuse non-excretory tissue such as the capsule and perirenal fat and the lining membranes of the calyces and pelvis; any reasonable allowance for these inactive channels leaves a negligible or zero volume to be accounted for as passing (uncleared) through the juxtamedullary glomeruli.

Senescence

Trueta and his colleagues suggest that, in elderly normal persons, protracted or repeated juxtamedullary diversion leads to canalization of glomeruli by degenerative vascular changes, with a consequent reduction in filtering surface and in the filtration rate. The studies of Davies and Shock [473] (ch. XVII) show that there is in fact a reduction in filtration rate with advancing age in man, but tubular tissue also degenerates, as shown by the progressive reduction in Tm_D, with no significant change in the C_{IN}/Tm_D ratio.

The effective renal plasma flow also suffers progressive decrease, the ratio C_D/Tm_D decreasing significantly in the older age groups. Our interpretation of these data is that with advancing age the entire renal parenchyma, glomeruli and tubules, undergoes senescent degeneration in a closely parallel manner, the renal plasma flow suffering a somewhat greater decrease because of arteriosclerosis or other vascular changes. If aglomerular nephrons exist in the senescent kidney, they are not sufficiently numerous to make themselves evident in these careful functional studies.

Essential Hypertension

The Oxford investigators have advanced the hypothesis that diversion of blood through the juxtamedullary circulation plays a role in the genesis of essential hypertension by rendering the renal cortex ischemic and thereby initiating or permitting the formation of a renal pressor substance. However, if a conclusion can be reached in this complicated problem, the evidence cited in chapter XXIII exculpates the kidneys in the genesis of essential hypertension. Moreover, the data on the extraction ratio of PAH, also cited in that chapter, show that this value is not reduced in hypertensive subjects until the disease has made serious inroads upon the renal arteriolar bed. Where the Oxford workers found the largest number of canalized glomeruli in the kidneys of hypertensive subjects (a circumstance that should reduce the filtration fraction and the extraction ratio of inulin), the facts are that in essential hypertension the filtration fraction is generally elevated, sometimes extraordinarily so, by the production of impotent nephrons. The few data available on the renal oxygen arterial-venous difference [329] do not indicate arterialization of the renal venous blood. We must, therefore, dismiss juxtamedullary diversion as in any way responsible for the genesis of this disease.

Adrenalin

Trueta and his colleagues elicited juxtamedullary shunting in the rabbit by the intravenous administration of adrenalin in doses of 0.1 to 0.17 mg/kg., and they suggest that the reduction in effective renal blood flow produced by physiologic doses of adrenalin in man is in part attributable to this phenomenon. Reubi and

Schroeder [1699] report that adrenalin (0.5 to 0.8 mg.) administered subcutaneously to man produced no significant change in E_{PAH} in the majority of subjects; the greatest decrease was 11.4 per cent. The oxygen arterial-venous difference decreased in 2 out of 5 instances, but not simultaneously with a decrease in E_{PAH}. Similar results were obtained with subcutaneous histamine (0 5 mg.) in 3 subjects, no changes occurring in E_{PAH} or E_{IN}.[1699] Dog experiments were inconclusive, but the authors conclude that substantial diversion cannot be elicited in man by physiological doses, or in dogs by larger doses of these drugs. In 2 experiments reported by Breed, Maxwell, and Smith,[210] E_{PAH} remained constant after the administration of 1.0 mg. of adrenalin (0.5 mg subcutaneous and 0.5 mg. intramuscularly), confirming the observations of the St. Louis investigators.

Syncope

Werkö, Bucht, and Josephson [2170] found no change in E_{PAH} during the renal ischemia induced by tilting. The oxygen arterial-venous difference increased rather than decreased during tilting.

Antidiuresis

Trueta *et al.* accept, as was proposed some years ago by Frey [697] and utilized by Fuchs and Popper [724] as an explanation of water diuresis, that diversion of blood through the juxtamedullary circuit plays a role in antidiuresis, since they obtained cortical ischemia by massive doses of pituitary extract in rabbits.

Corcoran and Page [411] found that in dogs pitressin in very large doses (8 to 100 milliunits/min.) over protracted periods increased the total renal plasma flow in 5 experiments (+16 to 90 per cent) and decreased it in 5 (−5 to 22 per cent) with no effect in an eleventh test E_{IN} increased by 19 to 91 per cent in 4 experiments, decreased by 10 to 31 per cent in 5, and showed less than 10 per cent change in 2. The direction of change was not related to dosage, but the largest increases in E_{IN} coincided with the largest decreases in total renal plasma flow, whereas the instances where E_{IN} decreased coincided with the greatest increase in plasma flow. In those experiments where E_{IN} increased or showed no change (6 out of 11) if blood was diverted through an extraglomerular circuit or through canalized glomeruli, a great increase in extrac-

tion ratio must have occurred in residual *functioning glomeruli.* The fact that in those instances where E_{IN} decreased, suggestive of diversion, the filtration rate remained unchanged or increased substantially, argues against a shunt.

The extraction ratio of phenol red was decreased by pitressin in only 4 out of 11 experiments, when it was reduced by 28 to 45 per cent, coincidently with marked *increases in plasma flow, but* in these instances the filtration rate increased from 2 to 34 per cent. If the decrease in E_{PR} was the result of diversion, it is difficult to see why the filtration rate should increase.

In only 3 out of the 11 tests did E_{PR} (−45, 28, and 32 per cent) and E_{IN} (−31, 10, and 24 per cent) decrease simultaneously by 10 per cent or more. In these 3 experiments there was a marked increase in plasma flow (+90, 64, and 75 per cent), and these might conceivably be interpreted as evidences of a shunt. The other 8, however, do not support this interpretation. In none of 6 experiments in which pitressin was given to atropinized dogs did E_{PR} and E_{IN} decrease simultaneously by 10 per cent or more.

These investigators found that the constant intravenous infusion of renin into dogs with explanted kidneys decreased the total renal plasma flow in 9 out of 10 experiments, the average decrease being −35 per cent (range −20 to −47 per cent). The effects upon E_{PR} were slight and of variable sign, averaging a 3 per cent increase. E_{IN} increased in 9 out of 10 instances (+9 to 108 per cent, average 50). Thus, renin, which produces marked renal ischemia, leaves the filtration rate unchanged, doubles the filtration fraction, and has no significant effect upon E_{PR}. There is in the dog, therefore, no evidence that pitressin in very large doses, or renin, produces a consistent reduction in the extraction ratio of phenol red or inulin, the first a certain, the second a probable, concomitant of juxtamedullary diversion.

Breed, Maxwell, and Smith [250] report that in 16 normal subjects with urine flows ranging from 0.68 to 15 cc/min., and under extremely variable and at times rapidly changing states of hydration, E_{PAH} remained within the range of 0.88 to 0.96. *In 1 instance,* when the urine flow fell from 13 to 2 cc/min., 3 successive extraction ratios were 0.93, 0.92, and 0.92. Renal oxygen arterial-venous

differences from 9 of these subjects were within the normal range and showed no relationship to urine flow.

It is impossible to duplicate in human subjects the massive doses of pitressin that the Oxford workers administered to their animals—0.2 to 20 pressor units/kg., equivalent on the basis of body weight to 14,000 to 1,400,000 milliunits in man; * and indeed it is questionable whether comparable amounts of antidiuretic hormone ever appear in the human or animal circulation. But Breed, Maxwell, and Smith have examined in 10 subjects the effects of more moderate doses of pitressin, which in such doses has no effect on the renal circulation (fig. 79, p. 431). Control observations were made during a period of water diuresis for at least 2, and usually more, clearance periods of 15 to 45 min. Further observations were made 30 min. after an intravenous injection of pitressin followed by a constant sustaining infusion of this hormone. In 7 experiments physiologic doses of pitressin [1218] were used, a priming dose of 50 milliunits and sustaining doses of 50 milliunits/hr. In 2 subjects pharmacologic doses were employed (5000 and 2000 milliunits/hr. respectively). In these 2 subjects the pitressin caused marked facial and mucosal pallor and complaints of faintness, abdominal cramps, and impending syncope. In all cases the effect of pitressin was manifested by a sudden reduction in urine flow and an increased U/P ratio of PAH.

Because of the possibility of rapid transient renal effects (with subsequent autonomic accommodation of the renal circulation), particular attention was given to the immediate effects of the hormone in 3 subjects. Extraction ratios were obtained 2, 9.5, and 2 min., respectively, after the injection of pitressin, during which time all 3 subjects were visibly pallid. Renal oxygen arterial-venous differences were obtained in these subjects 14, 8, and 1 min. after pitressin, while clearances were continued throughout the entire period of equilibration.

The PAH and inulin clearances showed no significant or constant changes following pitressin. E_{PAH} remained above the accepted lower normal limit of 0.88, varying in either direction by

* Antidiuresis may be maintained in man by the administration of less than 50 milliunits/hr

1 to 3 per cent in all subjects except one, in whom this value decreased by 5 per cent, scarcely a significant drop; the renal oxygen arterial-venous difference, however, coincidently increased in this subject. The renal oxygen arterial-venous difference and renal extraction of oxygen increased in 6 subjects and decreased in 3, these changes occurring independently of minor variations in clearances or extraction ratios. Extraction ratios of inulin were observed in only a few of these subjects because of the large technical error in this measurement. An analytical error of 3 or 4 per cent in the inulin analysis will cause wide variations in the calculation of E_{IN} where two fairly close blood levels are being compared. But in no case was there much change in this value. The observations of Breed *et al.* on the effects of pitressin in man are in agreement with those of Corcoran and Page [411] in dogs that received large amounts of pitressin over protracted periods and reveal no evidence of juxtamedullary diversion during spontaneous changes in urine flow or after the injection of pitressin.

Shock

Trueta and his colleagues were led into their study of the renal circulation in the rabbit by the problem of tourniquet shock, which represents their major method for eliciting juxtamedullary diversion in this species. They postulate that such diversion of blood away from effective exposure to glomerular filtering surface is responsible for the oliguria of shock in general.

No data on the extraction ratio of PAH in uncomplicated circulatory failure in man are as yet available, but Phillips, Dole, Hamilton, Emerson, Archibald, and Van Slyke [1464] found that, in acute hemorrhagic and traumatic shock in the dog, the kidneys continued to extract PAH with the same degree of completeness ($E_{PAH} = 0.87$) until the shock was so severe that the renal plasma flow was reduced to below 3 per cent of normal. Qualitatively similar observations have been reported by Corcoran and Page.[415] The fact that the renal oxygen arterial-venous difference did not increase with the late stages of shock in the dog,[531] in contrast to the immediate increase in oxygen extraction by the body as a whole, might be interpreted as indicative of diversion of blood through channels not presented to the renal parenchyma for clear-

ance; but the injection of dyes (India ink, Evans blue, and trypan blue) into the renal artery of 3 dogs during the terminal stages of shock revealed that the kidney was uniformly perfused, while histological examination of some of these kidneys revealed no instance of selective cortical ischemia (Oliver, pers. com.). Van Slyke,[2092] reviewing the experiments of the Rockefeller group on shock in dogs, rejects the diversion hypothesis, chiefly on the basis that the renal blood flow is decreased rather than increased as would be expected if capacious vascular channels were opened through the medulla.

Maluf[1378] rejects the interpretation relative to hemoglobinuric nephrosis because he found equal and normal (India ink) injection of the cortex and medulla following anuria and marked diminution of clearances In reversible shock in dogs he found a diminished injection of the entire kidney, with more dye in the cortex than in the medulla.

Anuria

In 4 subjects recovering from oliguria caused by inhalation carbon tetrachloride poisoning, Sirota[1903] demonstrated great reduction in renal blood flow, filtration rate, E_{PAH}, and E_{IN} during the early stages of spontaneous diuresis, with a gradual return of renal clearances toward normal during 100 to 200 days after the onset of the oliguria The renal oxygen arterial-venous difference in 1 subject on the seventeenth day was 3.0 cc/100 cc. He attributes the decreased extraction of PAH and inulin to tubular damage caused by anoxia, resulting in increased tubular permeability and unselective reabsorption of the glomerular filtrate.

Breed and Maxwell (pers. com.) have made observations during oliguria, which persisted for 6 days, in a subject suffering a post-transfusion reaction, and found E_{PAH} to be reduced to 0 06, with a renal oxygen arterial-venous difference of 2.5 cc/100 cc. Clearance studies at this time were so low as to be uninterpretable. Six days after the onset of diuresis, Tm_{PAH} was zero, and clearances of all substances measured were at the same very low level, indicating tubular reabsorption of all substances in the glomerular filtrate. Examination 102 days after the onset of oliguria showed E_{PAH} to be 0.90 and the renal oxygen arterial-venous difference to be 1.6 cc/100 cc., both within normal limits, although at this time the

1 to 3 per cent in all subjects except one, in whom this value decreased by 5 per cent, scarcely a significant drop; the renal oxygen arterial-venous difference, however, coincidently increased in this subject. The renal oxygen arterial-venous difference and renal extraction of oxygen increased in 6 subjects and decreased in 3, these changes occurring independently of minor variations in clearances or extraction ratios. Extraction ratios of inulin were observed in only a few of these subjects because of the large technical error in this measurement. An analytical error of 3 or 4 per cent in the inulin analysis will cause wide variations in the calculation of E_{IN} where two fairly close blood levels are being compared. But in no case was there much change in this value. The observations of Breed *et al.* on the effects of pitressin in man are in agreement with those of Corcoran and Page [411] in dogs that received large amounts of pitressin over protracted periods and reveal no evidence of juxtamedullary diversion during spontaneous changes in urine flow or after the injection of pitressin.

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Maluf[1378] rejects the interpretation relative to hemoglobinuric nephrosis because he found equal and normal (India ink) injection of the cortex and medulla following anuria and marked diminution of clearances. In reversible shock in dogs he found a diminished injection of the entire kidney, with more dye in the cortex than in the medulla

Anuria

In 4 subjects recovering from oliguria caused by inhalation carbon tetrachloride poisoning, Sirota[1903] demonstrated great reduction in renal blood flow, filtration rate, E_{PAH}, and E_{IN} during the early stages of spontaneous diuresis, with a gradual return of renal clearances toward normal during 100 to 200 days after the onset of the oliguria. The renal oxygen arterial-venous difference in 1 subject on the seventeenth day was 3.0 cc/100 cc. He attributes the decreased extraction of PAH and inulin to tubular damage caused by anoxia, resulting in increased tubular permeability and unselective reabsorption of the glomerular filtrate.

Breed and Maxwell (pers. com.) have made observations during oliguria, which persisted for 6 days, in a subject suffering a post-transfusion reaction, and found E_{PAH} to be reduced to 0.06, with a renal oxygen arterial-venous difference of 2.5 cc/100 cc. Clearance studies at this time were so low as to be uninterpretable. Six days after the onset of diuresis, Tm_{PAH} was zero, and clearances of all substances measured were at the same very low level, indicating tubular reabsorption of all substances in the glomerular filtrate. Examination 102 days after the onset of oliguria showed E_{PAH} to be 0.90 and the renal oxygen arterial-venous difference to be 1.6 cc/100 cc., both within normal limits, although at this time the

PAH and inulin clearances were less than 50 per cent of average normal values. These observations are consonant with non-perfusion of large and presumably damaged areas in the kidney, such tissue as is perfused functioning normally.

Clark, Barker, and Crosley[386] have reported on a patient anuric for 8 days following a transfusion reaction. The extraction ratios of creatinine, mannitol, urea, free PAH, and total PAH were 0.043, 0.050, 0.051, 0.017, and 0.080, respectively, all very subnormal and indicative of almost complete cessation of renal function. However, the oxygen arterial-venous difference was 1.53 cc/100 cc. and the CO_2 arterial-venous difference, +1.1 vols. per cent. These normal arterial-venous gas values indicate perfusion of metabolizing tissue rather than the operation of a by-pass. These authors suggest that an alternative interpretation might be the exclusive perfusion of non-excretory tissue which has a metabolic pattern characteristic of the kidney as a whole; but, since in the normal kidney non-excretory tissue receives no more than 10 per cent of the blood, it would be necessary to postulate complete ischemia for 9 days of 90 per cent of renal tissue in a patient who eventually recovered. They conclude that juxtamedullary diversion is untenable as an explanation of the anuria and infer that all the renal tissue is being slowly perfused and is extracting a normal amount of oxygen from each (unknown) volume of blood, but that excretory capacity has not yet been regained, because of either unselective reabsorption or tubular obstruction.

Although the evidence at present is not conclusive, it argues against the diversion of blood in man in oliguria of traumatic or toxic origin because (a) the renal blood flow is consistently reduced to very low levels, whereas if juxtamedullary diversion occurred this would not be the case; (b) the renal oxygen arterial-venous difference is increased, rather than decreased; (c) E_{PAH} recovers ahead of the PAH clearance, indicating that such blood as does perfuse the recovering kidney is cleared in the normal manner; and (d) there is no morphologic evidence of local cortical ischemia in kidneys from experimental or clinical cases. At the moment, the more probable explanation of acute renal failure is that given in chapter XXIV. Recovery of circulation and tubular func-

tion proceeds *pari passu*, so that at intermediate stages of recovery the blood is cleared in a normal manner.

Congestive Heart Failure

Although our present information on renal hemodynamics in chronic congestive heart failure was not available at the time the Oxford monograph was prepared, the greatly reduced renal blood flow and filtration rate in this condition would seem to make it a suitable circumstance for a by-pass to operate, if one exists. But the data cited in chapter XXII show that E_{PAH} is not reduced, while E_{IN} and the renal oxygen arterial-venous differences are increased in congestive failure, excluding the operation of a by-pass.

Abdominal Compression

Abdominal compression decreases renal blood flow, presumably by raising renal venous pressure. Bradley and Bradley [235] found E_{PAH} to average 0.923 in 8 subjects before compression, 0.929 during compression, and 0.932 (6 subjects) after compression was removed, and Bradley and Halperin [240] report no significant change in renal oxygen arterial-venous difference during compression.

In none of the foregoing clinical studies on man is there evidence of juxtamedullary diversion, and indeed in most instances (normal circulation, senescence, essential hypertension, adrenalin, syncope, antidiuresis, congestive heart failure, abdominal compression), the evidence is such as positively to exclude this phenomenon

Trueta *et al.* suggest that juxtamedullary diversion may be responsible for the pathological picture called 'lower nephron nephrosis,' but it has been pointed out in chapter XXIV that this term is somewhat inept, since the pathological changes in the anuric kidney are not restricted to the 'lower nephron' (distal segment). In any case, it is improbable that cortical ischemia sufficient to injure the distal tubule would fail to have adverse effects upon the proximal tubule intertwined with it.

Cortical ischemia with continued medullary perfusion is most clearly indicated in bilateral cortical necrosis, but most pathologists recognize that embolic occlusion of the renal arterioles plays

an important role in this disease (ch. XXI). To what extent the initial phase involves functional ischemia is not determined.

OBSERVATIONS IN THE RABBIT, DOG, AND CAT

Perfusion of the juxtamedullary circulation during cortical ischemia has been confirmed by some investigators in the rabbit, but has failed of confirmation in this species by others. In the dog, experiments have generally been negative.

Montague and Wilson [1486] have confirmed that 0.1 mg. adrenalin intravenously in anesthetized (nembutal-ether) rabbits produces juxtamedullary diversion, and they find that E_{PAH} decreases to a negative value averaging −0.266 in 7 animals, and returning to control levels (0.90) after 10 to 40 min. Reduction in E_{PAH} was also produced by shock in their experiments.

Cort and Barron [436] obtained juxtamedullary diversion in the rabbit and cat by reflex excitation and found that the initial response to stimulation of a spinal afferent is unilateral, becoming bilateral in 5 to 10 min. in cats, and 3 to 4.5 hr. in rabbits. The crossing occurs in the cord. Anuria can be relieved by novocainization of either the splanchnic fibers or of the spinal roots T10 to T12, and Stock [2013] reports that renal vasoconstriction can be blocked with tetraethylammonium bromide.

Hoff, Kell, Hastings, Gray, and Sholes [1020] have shown that these renal vasoconstrictor pathways are represented in the cerebral cortex of the cat (ch. XIV).

Arcadi and Farman,[57] injecting India ink into anesthetized (nembutal) rabbits, report that pilocarpine and magnesium sulphate, given intravenously, and water diuresis divert blood into the cortical circuit, whereas dehydration by Epsom salts, milk of magnesia, and croton oil diverts it into the juxtamedullary circuit. The effect of water diuresis and extreme (pathologic) dehydration as reported are contrary to the results obtained by Frey. The actions of pilocarpine and magnesium sulphate (dosage is not recorded) are difficult to interpret. The evidence shows that preferential perfusion may occur under extreme pharmacologic conditions, as after stimulation of the renal nerves.

Palmlöv [1673] reports juxtamedullary injection in the rabbit kid-

ney when the renal artery has been clamped for 1 hr. and 35 min., and after the injection of staphylococcus toxin.

Moyer, Conn, Markeley, and Schmidt [1494] confirm that in the rabbit stimulation of the sciatic nerve leads to renal ischemia (as measured by thermostromuhr, bubble flow meter, or the Barcroft-Brodie technique). However, the renal arterial-venous oxygen difference increased rather than decreased. Juxtamedullary diversion, as shown by India ink injection, could be produced in rabbits by adrenalin but not by sciatic nerve stimulation, while it could not be produced by either means in dogs, in which vasoconstriction was uniform throughout the kidney.

Black and Saunders [189] report that stimulation of the central end of the cut sciatic nerve for 10 to 20 min. reduced the PAH clearance in 5 out of 10 trials in rabbits The inulin clearance was less affected. The experiments are notable for the absence of any consistent effect in half of the rabbits, and cats proved to be even more resistant. In a second series of experiments, after laparotomy blood was diverted through plastic tubing from the renal vein to the jugular vein; after ligation of the inferior vena cava above and below the renal vein, diverted blood was drawn for the determination of extraction ratios. Rabbits stood the operation badly, but the investigators were able to observe 8 cats and 1 rabbit in which the renal venous blood flow was 10 cc/min. or more The control values of E_{PAH} were low (0.50 to 0.80), from which the authors infer that even before sciatic stimulation blood was diverted(?) from excretory tissue In 1 animal the renal venous pressure was observed on obstruction to rise to 70 cm. of water, far above normal maximal femoral or vena caval pressures (10 cm.), implying the opening of large communications between the renal artery and vein. E_{PAH} in this sample was 0.20. But after sciatic stimulation E_{PAH} was 0.77 and after pituitary extract, 0.80. The authors discuss the implications of their work with respect to a Trueta shunt, but draw no conclusions.

Hughes-Jones, Pickering, Sanderson, Scarborough, and Vandenbroucke,[1051] by the injection of Berlin blue into rabbits, found no evidence of medullary diversion of blood at the height of renal diuresis.

Kahn, Skeggs, and Shumway,[1086] using India ink injection, failed entirely to obtain evidence of juxtamedullary diversion in the rabbit under a variety of circumstances: in normal animals anesthetized with nembutal; during and after the action of adrenalin in doses (0.15 mg/kg.) sufficient to produce complete renal ischemia, as well as during the constant intravenous infusion of this compound; during and after the action of amyl nitrite by inhalation, renin, and angiotonin intravenously; and during hemorrhagic hypotension and stimulation of the central end of the cut sciatic nerve. Pitressin, renin, and angiotonin produced a picture of congestion of all glomeruli, efferent arterioles, and capillary components, including the *vasa recta*. Angiotonin in particular led to concentration of ink in the glomeruli, suggesting intense efferent arteriolar constriction. In 3 of 11 experiments involving sciatic nerve stimulation, the peripheral portions of the cortex were not filled with ink, unlike those deeper in the cortex and the juxtamedullary region. In these 3 animals the authors believe that marked constriction of the main renal arteries and their branches, including their arcuate portions, arrested perfusion in the parenchyma distally, so that only the first portions of the interlobular arteries and their dependent glomeruli were perfused.

Kahn and his coworkers suggest that failure to obtain India ink injection of certain areas, and particularly of the most peripheral cortical glomeruli and subcapsular capillaries, may sometimes be due to a rapid passage of blood which carries the ink into the veins that drain these regions. They also conclude that the most significant effect of amyl nitrite appears to be on the venous side, with marked dilatation of the cortical capillaries. The injected ink passes through the arterial side to accumulate in the dilated venous components of the *vasa recta*, the venous channels in the juxtamedullary zone, and in the venous end of the cortical intertubular capillaries, from which outflow is impeded by a rise in venous pressure. There was no evidence of a medullary by-pass in any of these experiments.

Goodwin, Sloan, and Scott [813] have failed in important respects to confirm the observations of Trueta and his coworkers in either rabbits or dogs. In numerous experiments involving tourniquet application or electrical stimulation of the central end of the di-

vided sciatic nerve (15 rabbits and 10 dogs anesthetized with nembutal or dial) only once did they observe unilateral cortical ischemia. The exception was a dog which had been subjected to intermittent stimulation of the central end of the left sciatic nerve for nearly 5 hr., which had been carrying a bladder cannula for many weeks, and in which bilateral calculi had formed in the renal pelves In several of these experiments bilateral total or partial ischemia of the kidneys was observed. Unilateral ischemia was obtained in rabbits, dogs, and monkeys consistently only after direct stimulation of the splanchnic or, better, the renal nerves. Under these conditions, the ischemia was most severe in the cortex, the juxtamedullary glomeruli being open to injection with dye or India ink. If the stimulus was of great intensity and duration, the kidney became totally ischemic. The authors hesitate to speak of the phenomenon as indicating a by-pass and say that it would be equally reasonable to explain the demonstrated cortical ischemia on the basis of total renal ischemia due to progressive vasoconstriction. They also remark that they are impressed with the hardiness with which the renal circulation withstands all assaults on the organism short of direct or indirect stimulation of the renal nerves

Maluf [1378] found no evidence, by the injection of India ink, that there is any diversion of blood from the cortex to the medulla during the oliguria induced by the injection of lysed red cells in the dehydrated dog.

Study and Shipley [2020] report that, after direct stimulation of the renal nerves in the dog, trypan blue is diffusely distributed in the kidney, with patchy, pyramidal areas of injection without preponderance of dye in the juxtamedullary areas

Draper and Whitehead [642] report that anuric dog kidneys, injected with colloidal mercuric sulphide at the height of reflex vasoconstriction elicited by respiratory arrest, are uniformly pigmented.

Houck [1040] obtained no evidence of juxtamedullary diversion after the injection of moderate doses (21 to 81 γ/kg. intravenously) of adrenalin in anesthetized (nembutal) dogs The filtration rate, urine flow, and renal plasma flow were decreased, but Tm_G was not affected. E_{PAH} remained normal at doses of 21

67 γ, but decreased by 30 per cent at 81 γ/kg. Tm_{PAH} was reduced by 30 per cent only at high doses. Houck concludes that, during the renal ischemia induced by moderate doses of adrenalin, no appreciable blood is diverted away from the cortex.

ARTERIAL-VENOUS ANASTOMOSES

Cargill [327] has attributed the decrease in E_{PAH} that follows the administration of serum albumin to man (ch. XIV) to diversion of blood through the juxtamedullary circulation. There is concomitantly a marked increase in renal plasma flow and a decrease in the corrected filtration fraction, but this is hemodynamically possible without positing juxtamedullary diversion. It is important to note that in every case the filtration rate increased, the average increase being 7 per cent (range 3 to 15 per cent), a fact that argues against diversion of blood from the cortex by any route.

Michie, Gimbel, and Riegel (ch. XIV) believe that the administration of albumin opens arterial-venous anastomoses without diverting blood away from the glomeruli, since they observed no change in filtration rate, PAH clearance, Tm_{PAH}, or Tm_G during the hyperemia and at a time when E_{PAH} was reduced. Barker, Clark, Crosley, and Cummins [87] confirm these observations with respect to filtration rate, PAH clearance, E_{PAH}, and Tm_{PAH} and concur in the conclusion reached by Michie *et al.* They find that the renal oxygen arterial-venous difference decreases by 30 to 40 per cent of the control value as the total renal blood flow increases, a fact that would be consonant with this interpretation.

The writer concurs, on the available evidence, in the belief that the renal hyperemia induced by albumin may represent the opening of some major non-excretory channels (arterial-venous anastomoses) which supplement the normal perfusion of the cortex without diverting blood in any significant degree from the cortex. It is probably by such channels that the glass spheres of Simkin, Bergman, Silver, and Prinzmetal [1896] pass from the arterial to the venous side of the renal circulation. If so, such non-excretory channels appear to be of slight functional importance, since they permit by-passing of at most a small fraction of the blood in the normal human kidney, and there is no evidence of their activity in any of the pharmacological or clinical circumstances cited above. How-

ever, there remains the possibility that these large doses of albumin may have an adverse effect on tubular excretion, decreasing E_{PAH} roughly in the same proportion as they increase the renal blood flow by action on the glomerular circulation.

THE SIGNIFICANCE OF THE MEDULLARY CIRCULATION

In summary, the positive evidence excludes the diversion of any appreciable quantity of blood through uncleared channels in senescence, essential hypertension, cardiac failure, or during the action of endogenous or exogenous antidiuretic hormone, adrenalin, histamine, pyrexial hyperemia in man, or in traumatic and hemorrhagic shock in the dog. There is no evidence of such diversion (and the data can be otherwise interpreted) in such oliguric states as have been examined in man.

That the kidneys are innervated by the sympathetic nervous system and that adequate excitation of afferent or efferent pathways will lead through these fibers, or through the action of adrenalin, to renal vasoconstriction has been known to numerous investigators since the time of Bradford (ch XIV). Differential constriction of the cortical glomeruli, as compared with the juxtamedullary glomeruli, in the rabbit has been demonstrated by Trueta and his colleagues, but only partially confirmed by other investigators The evidence suggests that the cat kidney responds like the rabbit kidney. But the phenomenon of by-passing has not been confirmed in the dog as yet, and the evidence, in a positive sense, quite excludes its existence in man in all the conditions enumerated above, if we accept the interpretation that the juxtamedullary circulation is unique in so far as the fate of the postglomerular blood is concerned.

Before attempting an interpretation of the paradoxes here presented, it must be remarked that the conditions under which juxtamedullary diversion has been elicited in the rabbit are traumatic in the extreme, and it may be that under comparably traumatic conditions the phenomenon might be elicited in man. Furthermore, we have repeatedly remarked that the sympathetic nervous system in the rabbit appears to be so highly labile that extreme renal vasoconstriction is readily induced in this species, in contrast to the dog and man. Accepting these arguments as signifi-

cant, the anatomical fact remains that the juxtamedullary glomeruli in man and the dog, as in the rabbit, do differ from the cortical glomeruli in respect to the fate of the postglomerular blood. It is on this difference that the Oxford investigators have rightly placed their emphasis.

We are left then with two questions: (a) what functional significance is to be attributed to the juxtamedullary circulation; and (b) is there any evidence which might explain a species difference in the vasomotor pattern of the kidney in various mammalian species?

With respect to (a), it should be noted that the straight limb of Henle's loop of those nephrons located in the juxtamedullary region penetrates the 'outer band' of the 'outer zone' of the medulla (Oliver, pers. com.),[1595] where it is surrounded by or admixed with *vasa recta;* only in the 'inner band' of the outer zone and the 'inner zone' of the medulla is the nephron represented exclusively by the thin segment (plate II, ch. I). The Oxford workers treat this straight (descending) limb as part of the 'loop of Henle,' which in a historical and anatomical sense is correct but is functionally misleading in that it implies functional equivalence with the thin segment. These thick-walled tubules are anatomically similar to the proximal convoluted tubules and must be considered functionally as proximal tubular tissue. Thus, even if the efferent blood from the juxtamedullary glomeruli is restricted wholly to the *vasa recta*, and if the *vasa recta* have no capillary offshoots, this proximal tissue in the descending limb of the loop of Henle could extract PAH from this blood in a normal manner, for it is in intimate relation with both the descending and ascending portions of the *vasa recta*. On the other hand, the thin limb terminates in a thick ascending limb which may be of considerable length within the medulla; if this segment is functionally identical with distal convoluted tubular tissue, and one may presume it is, it could perform the reabsorptive functions usually ascribed to the latter. In brief, the vascular-tubular relations in the outer medulla are such as to permit essentially the same clearance functions for the juxtamedullary glomeruli as for the cortical glomeruli.

An alternative interpretation is that such anatomical peculiarities of the medullary circulation as might militate against proximal tubular clearance are nullified by the peripheral movement

of interstitial fluid. It has been suggested [724] that in the medulla *interstitial fluid moves toward the cortex; if this flow actually* translates fluid from around the *vasa recta* to the inner zone of the cortex, or even *the outer zone of the medulla, this might bring the fluid into contact with* proximal tissue and suffice to effect clearance of such juxtamedullary blood as is *not directly presented* to this tissue. The juxtamedullary *nephrons could function* qualitatively *and quantitatively like cortical nephrons* except under *circumstances* where the circulation of interstitial fluid was impeded, as perhaps might occur *in renal edema, perinephritis*, and other circumstances raising intrarenal pressure. There is evidence that *in conditions involving* partial injury of the parenchyma vicarious clearance of this type can be of a *considerable order* of magnitude, but it has not been established whether this vicarious clearance is attributable *to diffusion or to circulation* of interstitial fluid.[738, 1939] We *believe*, however, *that* the hypothesis of circulation of interstitial fluid should be advanced *cautiously until* more is known about this *largely neglected functional* aspect of the renal circulation.

If either (or both) of the foregoing views is accepted, exclusive perfusion of the juxtamedullary *glomeruli would make little* difference in the fate of the blood so far as renal clearance is concerned. *We are then left with the important* question: what is the *physiological significance of the* renal medulla, with its striking anatomical composition of an assemblage *of the thin segments* of the loops of Henle (*particularly belonging to the* juxtamedullary nephrons) and *of the parallel and* extremely abundant *vasa recta?* A 'medulla' *having something of* this anatomical composition appears *to be developed to a greater* or lesser extent in all the mammals and in the birds, the two Classes *in which the thin* segment is more than a *short connecting piece* between the proximal and distal segments.

That *the medulla is not concerned* primarily with water diuresis can be argued from *comparative physiology: the excretion* of an osmotically dilute urine occurs in *the fresh-water* elasmobranch and teleost fishes, *Amphibia and reptiles*, where no thin limb or *medulla is developed. As has long been* recognized, the presence *of the thin limb is correlated* with the capacity to elabo-

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If either (or both) of the foregoing views is accepted, exclusive perfusion of the juxtamedullary glomeruli would make little difference in the fate of the blood so far as renal clearance is concerned. We are then left with the important question: what is the physiological significance of the renal medulla, with its striking anatomical composition of an assemblage of the thin segments of the loops of Henle (particularly belonging to the juxtamedullary nephrons) and of the parallel and extremely abundant *vasa recta*? A 'medulla' having something of this anatomical composition appears to be developed to a greater or lesser extent in all the mammals and in the birds, the two Classes in which the thin segment is more than a short connecting piece between the proximal and distal segments.

That the medulla is not concerned primarily with water diuresis can be argued from comparative physiology: the excretion of an osmotically dilute urine occurs in the fresh-water elasmobranch and teleost fishes, Amphibia and reptiles, where no thin limb or medulla is developed As has long been recognized, the presence of the thin limb is correlated with the capacity to elabo-

cant, the anatomical fact remains that the juxtamedullary glomeruli in man and the dog, as in the rabbit, do differ from the cortical glomeruli in respect to the fate of the postglomerular blood. It is on this difference that the Oxford investigators have rightly placed their emphasis.

We are left then with two questions: (a) what functional significance is to be attributed to the juxtamedullary circulation; and (b) is there any evidence which might explain a species difference in the vasomotor pattern of the kidney in various mammalian species?

With respect to (a), it should be noted that the straight limb of Henle's loop of those nephrons located in the juxtamedullary region penetrates the 'outer band' of the 'outer zone' of the medulla (Oliver, pers. com.),[1595] where it is surrounded by or admixed with *vasa recta;* only in the 'inner band' of the outer zone and the 'inner zone' of the medulla is the nephron represented exclusively by the thin segment (plate II, ch. I). The Oxford workers treat this straight (descending) limb as part of the 'loop of Henle,' which in a historical and anatomical sense is correct but is functionally misleading in that it implies functional equivalence with the thin segment. These thick-walled tubules are anatomically similar to the proximal convoluted tubules and must be considered functionally as proximal tubular tissue. Thus, even if the efferent blood from the juxtamedullary glomeruli is restricted wholly to the *vasa recta,* and if the *vasa recta* have no capillary offshoots, this proximal tissue in the descending limb of the loop of Henle could extract PAH from this blood in a normal manner, for it is in intimate relation with both the descending and ascending portions of the *vasa recta.* On the other hand, the thin limb terminates in a thick ascending limb which may be of considerable length within the medulla; if this segment is functionally identical with distal convoluted tubular tissue, and one may presume it is, it could perform the reabsorptive functions usually ascribed to the latter. In brief, the vascular-tubular relations in the outer medulla are such as to permit essentially the same clearance functions for the juxtamedullary glomeruli as for the cortical glomeruli.

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of interstitial fluid. It has been suggested [724] that in the medulla interstitial fluid moves toward the cortex; if this flow actually translates fluid from around the *vasa recta* to the inner zone of the cortex, or even the outer zone of the medulla, this might bring the fluid into contact with proximal tissue and suffice to effect clearance of such juxtamedullary blood as is not directly presented to this tissue. The juxtamedullary nephrons could function qualitatively and quantitatively like cortical nephrons except under circumstances where the circulation of interstitial fluid was impeded, as perhaps might occur in renal edema, perinephritis, and other circumstances raising intrarenal pressure. There is evidence that in conditions involving partial injury of the parenchyma vicarious clearance of this type can be of a considerable order of magnitude, but it has not been established whether this vicarious clearance is attributable to diffusion or to circulation of interstitial fluid.[795,1939] We believe, however, that the hypothesis of circulation of interstitial fluid should be advanced cautiously until more is known about this largely neglected functional aspect of the renal circulation.

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rate a hypertonic urine; and, as stated in chapter XI, we conceive that it is a sort of safety diffusion mechanism insuring that the distal system will receive urine in which salt and water occur in constant, fixed proportions, a matter of some importance if the distal reabsorption of sodium and water is limited by critical constants. As glomerular filtration has acquired increased importance in the mammals (as compared with the reptiles and Amphibia), an advantage accrues from elaboration of both the thin limb and the necessary reabsorbent capillary channels in the form of the *vasa recta*.

From our knowledge of the high value of E_{PAH} in man, we must infer either that only a small fraction (probably less than 5 per cent) of the renal blood normally perfuses the juxtamedullary glomeruli and the *vasa recta*, or that the relations of the proximal and distal tubules to the *vasa recta*, supplemented perhaps by circulation of interstitial fluid, are such as to effect the same clearance and reabsorptive operations as are carried out upon the capillary blood in the cortex. The first inference is so improbable that perforce we must accept the second. In this case, the juxtamedullary circulation is anatomically but not physiologically unique.

There remains the fact that sometimes during renal ischemia in the rabbit, and perhaps to some extent in other mammals, the juxtamedullary nephrons may continue under perfusion when the cortical nephrons are devoid of blood. In seeking an answer to this species difference in the pattern of vasomotor response, we should like to call attention to certain features in the development of the mammalian kidney described in chapter XVI.

In newborn infants the filtration rate, the effective renal plasma flow, and Tm_{PAH} are all low on a surface area basis and increase to adult values between the first and second year of life, reflecting the rapid maturation of the infant kidney. The persistence of cuboidal fetal glomerular membranes doubtless reduces the filtration rate, but despite a low filtration rate the filtration fraction is excessively high (0.40 to 0.60), implying (as one explanation) a low value of E_{PAH}. Furthermore, the C_{IN}/Tm_{PAH} and C_{PAH}/Tm_{PAH} ratios are characteristically supernormal. In infancy and until late in childhood the cortex/medulla thickness ratio is lower than in the adult. The renal circulation at birth appears to be pre-

dominantly a glomerular one, despite the low value of the filtration rate on a surface area basis This may be because the postglomerular blood escapes into the venous circulation without tubular clearance, for the reason that an adequate quantity of proximal tubular tissue or an adequate circulation to that tissue is not yet developed. This circumstance would lead to a low extraction of diodrast and PAH, to low clearances of these compounds, to low values of Tm_{PAH} on a surface area basis, to a high filtration fraction, and to a high C_{IN}/Tm_{PAH} and possibly a high C_{PAH}/Tm_{PAH} ratio. As proximal tissue develops in the first year r so of life, all postglomerular blood comes ultimately to be presented to proximal tissue for clearance, and E_{PAH}, C_{PAH}, and Tm_{PAH} increase, while the filtration fraction and C_{IN}/Tm_{PAH} decrease to their adult values.

In view of the fact that the juxtamedullary nephrons develop ahead of the cortical nephrons in all mammals, it is possible that much of the neonatal circulation is through the *vasa recta*, a circumstance conducive to the maximal conservation of water but not conducive to maximal filtration or tubular clearance

In the white rat (and in the rabbit?) the number of glomeruli double after birth, but man (and the dog?) are born with their full complement of glomeruli It may be that the primordial (fetal) juxtamedullary glomeruli in the rat (and rabbit?) receive a meager sympathetic innervation (for which there is little or no requirement during fetal life), while glomeruli in the neogenic zone, developing in late fetal life or after birth, establish more effective sympathetic connections and are more susceptible to neurogenic vasoconstriction Whereas, if all the glomeruli in man (and dog?) are differentiated at birth, whatever sympathetic connections are established with them are less likely to reflect postnatal development of the cortex Alternatively, neuromotor imbalance between cortex and juxtamedullary region may represent a fetal pattern that is variably lost in the adults of various species In ther view, the juxtamedullary circulation would represent a scular area refractory to neurogenic vasoconstriction in some ecies and not in others, but otherwise having no unique funcnal significance other than to promote the reabsorption of ter from the thin segment.

CHAPTER XXVI

Diseases of the Kidney and Urinary Tract

GLOMERULONEPHRITIS

Glomerulonephritis is a bilateral renal disease which has as variable signs the abrupt onset of edema, proteinuria or hematuria, renal functional impairment, and hypertension. The disease appears in acute and chronic forms, and it is generally accepted that these are etiologically related. Chronic glomerulonephritis is subject to exacerbations following infection With few exceptions, investigators consider the nephrotic syndrome (nephrosis) as an intermediate stage.

The evidence indicates that acute glomerulonephritis is a sequella of infection with group A hemolytic streptococcus (tonsillitis, laryngitis, paranasal sinusitis, otitis media, cervical adenitis, scarlet fever, etc.). The evidence also incriminates Streptococcus viridans (in subacute bacterial endocarditis) and the pneumococcus. The disease usually makes its appearance after an asymptomatic latent period ranging from a few days to 4 weeks, the *average interval being 12 days, this latent period representing* an interval during which immunological reactions, possibly akin to allergy or sensitization, result in vascular changes of sufficient severity to reach the threshold of discovery. In this respect acute nephritis presents a parallel to rheumatic fever, where obvious organic involvement follows acute infection by a week or more.

Second attacks of acute glomerulonephritis are extremely rare. Usually the earliest recognized signs are urinary abnormalities, edema, and hypertension; in a small and equal proportion of instances only urinary abnormalities and edema, urinary abnormalities and hypertension, or urinary abnormalities alone may be present. In rarer instances edema and hypertension may occur without albuminuria or other evidence of renal involvement, a circumstance which leads some to believe that the functional changes in nephritis involve the circulatory system as a whole.[453, 886, 1559]

In the majority of patients the most evident focus of reaction is in the kidney, where it involves the glomeruli. The outstanding histological changes involve the visceral capsule and basement membrane of the glomerulus, which becomes thickened and occluded by increased cellularity owing to multiplication of the intercalated cells in the axial space between the capillary loops. The arterioles and tubules are not at first involved, but with progressive obliteration of the glomerular circulation by fibrosis the dependent parenchyma undergoes degenerative changes and gradual if irregular extinction of the entire nephron occurs. The glomerular lesion is accompanied by hematuria or hemoglobinuria, and the appearance of leucocytes, hyalin, granular, and cellular casts and desquamated tubular epithelium in the urine. Urinary volume may be normal or may be replaced by oliguria. The acute disease usually runs its course in less than a month, the end being marked by disappearance of edema, subsidence of hypertension and azotemia where these are present, and in the most favorable cases by the disappearance from the urine of all signs of a glomerular lesion. In the majority of patients, especially among children, recovery appears to be complete and without tendency to recurrence.

In less fortunate instances, for reasons unknown, proteinuria, microscopic hematuria, and impaired concentrating power persist, revealing a subacute or chronic process. Complete recovery fails to be effected, and the disease takes the form of chronic *glomerulonephritis in which hyalinization and fibrosis of the glomerular tuft* gradually obliterate the glomerular circulation and, perhaps as a consequence or perhaps independently, tubular tissue, while arteriolar lesions destroy the vascular tree, this chronic

degenerative process running an inexorable course until the destruction of renal parenchyma leads to contracted kidneys composed mostly of scar tissue and tubular *detritus.*

In the kidney of chronic glomerulonephritis every nephron may differ from its neighbor in structure and presumably in function Some undergo hypertrophy, as after subtotal nephrectomy, and in experimental nephritis it has been shown that the proximal tubule cells in such hypertrophic nephrons take up the vital dye, trypan blue; but it has not been shown whether the dye gains access to the cell from the blood or by way of the lumen, nor is it demonstrated to what extent cells capable of vital staining are active in tubular excretion or reabsorption. Nephrons of abnormal structure, with atrophied and atypical epithelium, absorb and store the dye poorly or not at all. Obstruction of the lumen by protein casts undoubtedly plays an important role in causing the ultimate degeneration of some nephrons.[1549, 1550]

Several studies of renal disease have included observations on the filtration rate and renal plasma flow in individuals with acute or chronic glomerulonephritis,[259, 328, 329, 432, 648, 733, 893, 1001, 1003, 1449, 1999] which demonstrate that the filtration rate and renal plasma flow may be variably reduced and terminally are of course reduced to very low values.

Considerable clarification is effected by analyzing these functional changes in relation to the quantity of residual functional tissue as measured by Tm_D, as was done in the study of Earle, Taggart, and Shannon.[565] In view of the primary nature of the glomerular lesion, it is not surprising that the most characteristic functional change is a reduction of filtration rate, best revealed by the C_F/Tm_D ratio. Figure 146 shows the mannitol * clearance in relation to Tm_D in 22 patients studied in various stages of the disease, from active or healed glomerulonephritis to terminal uremia. The data appear to give a fair cross-sectional view of the

* *The mannitol clearances* are uncorrected for the discrepancy between the mannitol and inulin clearances subsequently reported by Earle and others [illegible] this study obtained a mannitol/inulin [illegible] (range 0 97 [illegible] echnique of analysis and is minimal with the analy[illegible]eir mannitol clearances have been accepted without correction

effects of the disease on the functional organization of the kidneys. Except in terminal states, the ratio C_F/Tm_D is below the mean normal value, showing the extent to which the filtration bed is

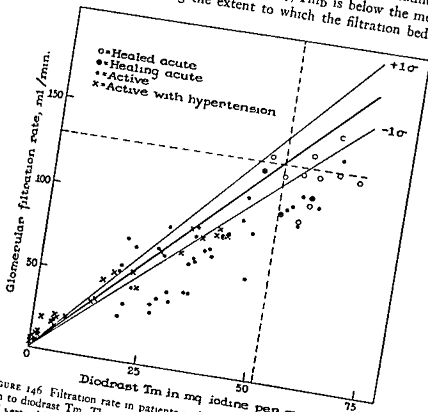


FIGURE 146 Filtration rate in patients with diffuse glomerulonephritis in relation to diodrast Tm The mean normal values are indicated by the horizontal and vertical lines The normal relation [781] between them (C_F/Tm_D) is extrapolated to zero by the solid diagonal line Data obtained after healing of an acute diffuse glomerulonephritis are indicated by open circles, those obtained during healing or probable healing by dotted circles, and the remainder (active) by solid circles, or by crosses when the diastolic blood pressure was in excess of 90 mm. of Hg (Earle, Taggart, and Shannon [88])

specifically affected. Late in the disease, when Tm_D has been reduced to very low values, tubular injury runs ahead and such nephrons as remain approach the impotent category, contributing little to the glomerular filtrate in the way of excretion and probably

ably little in the way of reabsorption. It is plausible to believe that this ultimate destruction of tubular function is related to ischemia issuing from the widespread destruction of the collateral vascular and capillary system.

In patients with hypertension (i.e. diastolic pressure above 90 mm. Hg) the ratio C_F/Tm_D is no greater than in patients without hypertension, implying that hypertension is ineffective in increasing the filtration rate, presumably because of the increased barrier to filtration created by thickening of the glomerular membranes.

The interpretation of the diodrast or PAH clearance in nephritis is complicated by a marked reduction in the extraction ratio of these compounds as the renal parenchyma is destroyed. Bradley, Curry, and Bradley [229] obtained values of E_{PAH} ranging from 0.58 to 0.76 in 6 subjects with chronic glomerulonephritis, and Bradley [231] reports values ranging from 0.47 to 1.00 in 9 subjects with acute nephritis. Cargill [325] reports E_{PAH} in 8 subjects with chronic glomerulonephritis in whom C_{PAH} was 455 or more as 0.84 (0.79 to 0.90), but in 3 subjects, in whom C_{PAH} ranged from 293 down to 90, E_{PAH} ranged from 0.64 to 0.35. He believes that E_{PAH} does not begin to decrease until C_F has fallen below 60 cc. and C_{PAH} below 300 cc.

In the absence of better information, it may be supposed that, in the disorganization of the vascular pattern in glomerulonephritis, channels are established whereby some blood may flow directly from the arterial to the venous side without exposure to functional tubular tissue. Such would be the case if episodes of protracted anoxia destroyed the excretory power in some tubules so that efferent glomerular blood escaped uncleared (impotent tubules as described on p. 606); while such a situation would probably be accompanied by glomerular degeneration and possibly canalization of defunct glomeruli. The studies of Oliver [1349] and others point to the development of paraglomerular vessels, relatively infrequent in the normal kidney, and to the persistence of function in relatively aglomerular tubules. However, the demonstrated reduction in E_{PAH} shows that such functional aglomerular tubules are overshadowed by atubular or glomerular vascular

channels. In the overall functional picture it is not aglomerular tubules that predominate, but atubular glomeruli.

Whatever the mechanism, the fact that E_D and E_{PAH} may be slightly reduced early in the disease and markedly reduced later must be kept in mind in interpreting renal clearances. Earle, Taggart, and Shannon hold suspect diodrast clearances in all subjects with Tm_D less than 6 mg of iodine, because they recognize that E_D might be reduced and that the diodrast clearance would have no certain relation to total renal plasma flow. A Tm_D of 6 mg. or below is observed in subjects with a diodrast clearance of 230 cc or less, a figure slightly below the critical level of 300 suggested by Cargill as that at which E_{PAH} may be expected to be reduced. But in the majority of subjects studied by Earle and his coworkers, the diodrast clearance may be accepted as closely reflecting total renal plasma flow.

In sharp contrast to the early reduction in filtration rate, the renal plasma flow per unit of tubular excretory tissue (C_D/Tm_D) in the subjects studied by Earle *et al* tends to remain normal, or, in many instances, to be substantially increased (fig. 147). No matter how much E_D may have been reduced, the residual functional tubular tissue is clearing a supernormal quantity of blood. This probably in part reflects vicarious clearance of efferent blood from glomeruli the tubules of which have lost their excretory power. That such blood should become available for clearance by residual functional nephrons (through circulation of interstitial fluid, etc., as pointed out in chapter XIX) does not contradict the suggestion that ischemia is responsible for the injury of other tubules; the interstitial fluid in any one area would in general flow in only one direction, and in this movement it may sweep through areas of low oxygen tension toward areas of normal oxygen tension. Moreover, the changes in the glomeruli in the acute stage and probably in the chronic stage of the disease appear to create a greater barrier to filtration than to the transit of blood, as would be implied by the low filtration fraction in many patients in whom Tm_D is still in the normal range. Thus both factors—impotent nephrons and thickening of the glomerular membranes—could operate to increase the perfusion of residual functional tissue.

Compensatory vasodilatation in residual functional glomeruli cannot, however, be excluded as a contributory factor.

Hypertension, which contributes little to overcoming the glo-

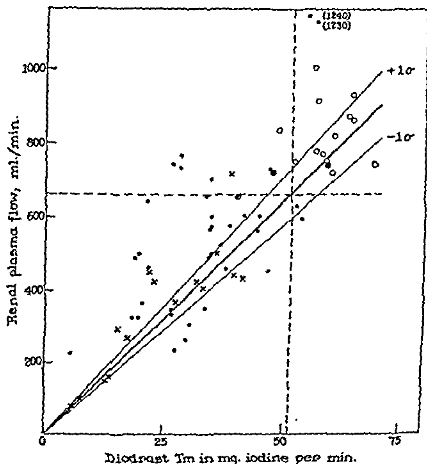


Figure 147. Renal plasma flow in patients with diffuse glomerulonephritis in relation to diodrast Tm. The mean normal value is shown extrapolated to zero. (Earle, Taggart, and Shannon [44])

merular lesion in figure 146, is also ineffective in increasing the renal plasma flow to the residual functional tissue, the ratio C_D/Tm_D being the same range in subjects with hypertension as in those with normal blood pressure. Except perhaps in the very late stages of the disease (Tm_D below 6.0), it is impossible to

look upon hypertension as a compensatory reaction serving to increase the renal blood flow in a scarred kidney; much greater degrees of hyperemia exist in patients without hypertension and in whom the kidney has suffered little damage, i.e. renal hyperemia when present appears to be the result of functional disturbances in arteriolar tone.

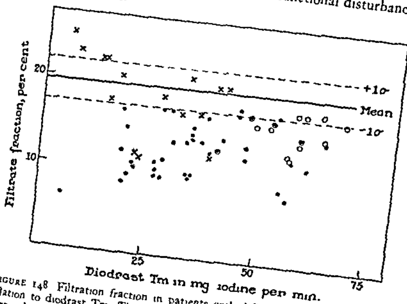


FIGURE 148 Filtration fraction in patients with diffuse glomerulonephritis in relation to diodrast Tm. The mean normal value is shown extrapolated to a zero value of diodrast Tm (Earle, Taggart, and Shannon [114])

Reduction in filtration rate, coupled with normal or increased renal plasma flow, leads to a reduced filtration fraction, as shown in figure 148. There is a strong suggestion that hypertension may increase the filtration rate at a given renal plasma flow and thus increase the filtration fraction, despite the fact that it fails to increase the plasma flow at a given degree of renal injury (as judged by reduction in Tm_D); the two ideas are not incompatible, for in such glomeruli as are still available to perfusion hypertension can raise the filtration rate but it cannot increase perfusion in obliterated tissue.

Since in the normal subject changes in renal plasma flow are not accompanied by proportional changes in filtration rate (ch.

XVIII), *the filtration fraction bears an inverse relationship to the* perfusion ratio, C_D/Tm_D, as shown in figure 113 on page 594. When the filtration fraction is plotted against this ratio in subjects with nephritis, as in figure 149, it will be seen that the filtration fraction is characteristically low and the perfusion ratio itself

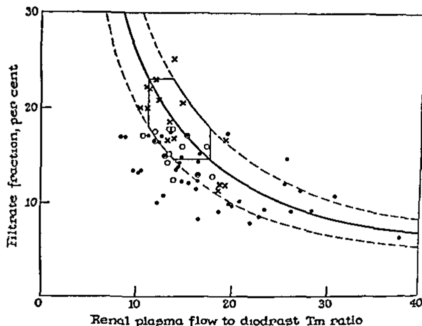


FIGURE 149. Filtration fraction in patients with diffuse glomerulonephritis in relation to renal plasma flow per unit of tubular excretory tissue (diodrast Tm) The normal parameters are those given in figure 115 for basal conditions (hexagon), the action of adrenalin and pyrexial hyperemia. (Earle, Taggart, and *Shannon* [165])

is frequently high; this one diagram dramatically depicts the two significant functional changes: reduction of filtration rate and hyperemia of the residual functional tissue. This figure, and figures 146 and 147, can profitably be compared with figures 129, *126, and 125, showing the normal relations and the* functional changes in hypertensive disease where the kidneys are only secondarily involved.

Earle and his coworkers were unable from their data to differentiate those patients who would recover from acute nephritis and those who were destined to pass into the chronic disease.

Recovery or failure of recovery cannot be correlated with the degree of renal functional damage as measured by available methods, but apparently depends upon obscure immunological or other factors. Where recovery occurs, renal function is restored, sometimes slowly, sometimes rapidly, to normal. Although in patients with chronic disease the filtration rate and Tm_D tend to decline, in a few renal function may improve while under observation. The authors suggest such cases may represent recovery from undetected exacerbations.

Hypertension is not necessarily related to a reduction of Tm_D, except that elevation of blood pressure appears more commonly late in chronic disease. Diastolic hypertension did not occur regularly in the patients studied by Earle *et al* until Tm_D was reduced to or below 20 mg of iodine.

Hilden[1000,1001] has reported urea and diodrast clearances (subcutaneous method) in 20 cases of acute and 26 cases of chronic glomerulonephritis. In only 1 instance of the acute disease did he see an initial clearance more than 10 per cent above the mean normal value, though 12 patients had initial clearances within the range of 80 to 110 per cent of this mean. In the rest, the initial clearance was low (24 to 80 per cent) and returned in the course of 1 to 3 months to the normal range.

In normal subjects, Hilden finds an average urea/diodrast clearance ratio of 0.12 (range 0.106 to 0.138). In observations made early in acute glomerulonephritis, this ratio was depressed in 18 out of 20 patients, reaching a low value of 0.043. The urea clearance tended to recover toward the normal value more rapidly than the diodrast clearance, so that the clearance ratio rose, in all but 3 instances reaching the normal range. Hilden attributes the reduction in this clearance ratio to impaired filtration, an interpretation which is consonant with the changes in the inulin clearance reported by Earle *et al*. However, Earle (pers. com.) finds that in some patients in the early acute phase, the urea/inulin clearance ratio may be excessively reduced (0.27 to 0.50) at very substantial urine volumes (0.62 to 6.09 cc/min.), a fact he attributes to excessive back diffusion, and this possibility must not be overlooked in interpreting low urea clearances and low urea/diodrast clearance ratios.

After recovery from the acute stage, the urea and diodrast clearances and the clearance ratio were normal or nearly so in all except one of Hilden's patients, who showed considerable impairment after 115 days. In another, a low urea clearance persisted after 91 days, implying permanent glomerular damage.

In the patients with chronic glomerulonephritis studied by Hilden, the urea and diodrast clearances ranged from normal to very low values. In the two most severely affected patients the diodrast clearance was 2 per cent, the urea clearance 6 per cent of normal. The urea/diodrast clearance ratio increased, in general, with deterioration of renal function, reaching values as high as 0.44. The phenomenon perhaps reflects the fact that, as concentrating power is lost and the average inulin U/P ratio decreases, less urea is absorbed and the urea/inulin clearance ratio rises from its normal value of 0.60 towards 1.0.

Hilden reports that the diodrast clearance is decreased to a lesser extent in patients with nephrosis (nephrotic type) than in those with hypertension (hypertensive type).

Black, Platt, Rowlands, and Varley [183] report inulin, urea, and diodrast clearances on 3 patients early in acute nephritis, with hematuria and hypertension. All clearances were subnormal, but the filtration fraction was again low (0.125, 0.118, and 0.09), showing excessive reduction of the filtration rate. With recovery, the inulin clearance and filtration fraction rose to normal in 2 patients in whom serial observations were made. The authors believe that their data cannot be interpreted in terms of a Trueta by-pass. They argue against decreased glomerular permeability as explaining the reduced filtration fraction on the grounds that inflamed capillaries are in general more permeable than normal, and the presence of albuminuria and hematuria implies increased permeability. On the contrary, the glomerular lesion is such as to reduce the extensive filtering surface of the normal glomerulus but grossly to increase its permeability at limited points to protein and even blood. The changes in the glomerular permeability coefficient are probably too great to warrant the application of hemodynamic equations to the problem of afferent and efferent tone.

A similar functional pattern is revealed in 9 patients with acute or chronic glomerulonephritis reported by Corcoran, Taylor, and

Page.[432] The filtration fraction and C_{IN}/Tm_D ratio were consistently low until terminal stages were reached, as judged by low values of Tm_D.

Hogeman[1024] records the following data on 51 men with acute nephritis: * inulin clearance 92 ± 34.7, diodrast clearance 390 ± 108, filtration fraction 0 234 ± 0.064, renal blood flow 671 ± 27.9; in 38 women these figures were 80 ± 32.6, 323 ± 111, 0 252 ± 0 072, and 539 ± 192. The data show lower renal function in those patients with a systolic blood pressure above 160 mm. Hg and a diastolic pressure above 100 mm. Hg, in those with a blood NPN concentration above 40 mg/100 cc., and in those who failed to recover within 3 months. It is interesting that the filtration rate averaged 78 9 in men and 69.2 in women with edema, and 99.8 in men and 94 3 in women without edema. Those who did not recover within 3 months had generally lower clearances.

Hogeman's data on chronic glomerulonephritis in 25 men give an average inulin clearance of 43 7 ± 27.9, diodrast clearance 173 ± 116, filtration fraction 0 270 ± 0 079, and renal blood flow 292 ± 200 In 23 women these figures were 44.9 ± 28, 172 ± 103, 0 280 ± 0.084, and 270 ± 168. The data show lower renal function when retinal changes are marked, when the systolic pressure exceeds 190 mm and the diastolic pressure 100 mm. Hg, and NPN exceeds 40 mg/100 cc.

Of 4 patients studied in the acute phase by Earle *et al*, 3 showed relative hyperemia, as judged by a C_D/Tm_D ratio more than 2σ above the normal mean. Relative hyperemia was observed in 1 of the 2 instances of exacerbation. In subsequent studies Earle (pers com.) has observed a significantly high C_{PAH}/Tm_{PAH} or C_{PAH}/Tm_G ratio in 5 out of 10 instances of acute glomerulonephritis but in none of 3 exacerbations. It appears that in some instances there is a phase of the disease in which there is marked renal hyperemia.

It has been held that pregnancy aggravates chronic glomerulonephritis, but Wellen, Welsh, Taylor, and Rosenthal[2142] found that 2 patients completed their pregnancy and were delivered at

* Mean values are not very meaningful in describing renal function in progressive renal disease, but the data show reduction in function as reported by others

term of normal children without increase in hypertension or proteinuria and without evidence of abrupt progression of the renal lesion as the result of pregnancy. Tm_D, when examined 1 and 2 years respectively after delivery, had decreased as compared with the values observed during pregnancy, but this decrease is consistent with the slowly progressive course of this disease

In a series of 12 subjects with acute nephritis reported by Bradley,[231] the mannitol clearance was below normal in all but 2 (90 and 157 cc.), ranging from 13.8 to 84.8 cc. The PAH clearance was reduced to a somewhat lesser extent, the filtration fraction as calculated from the unadjusted clearance generally being subnormal (0.08 to 0.17). However, E_{PAH} was reduced in 7 out of 9 subjects (0.470 to 0.829), the other 2 subjects (E_{PAH} of 0.94 and 1.00) having recovered completely according to the clinical evidence. Consequently the total renal plasma flow was substantially greater in nearly all subjects than was indicated by the PAH clearance, and in some it had a high normal or supernormal value. One subject, in whom E_{PAH} was 1.0, had the PAH clearance of 1320 cc/min., nearly twice the normal value. This renal hyperemia is reminiscent of the hyperemia known to accompany inflammation in other tissues, and may be related to the flank or back pain frequently present in the disease. Whether renal edema is present or not is unknown.

It is clear from Bradley's data that, as Earle, Taggart, and Shannon surmised, in chronic nephritis reduction of E_{PAH} may lead to a wide discrepancy between the PAH clearance and the total renal plasma flow. Tm_{PAH} was determined in 8 subjects and was reduced in all but 1, though the data do not permit an inference with respect to the critical value of Tm_{PAH} (or of C_F) at which E_{PAH} breaks. More data are needed on this point.

Bradley concludes that the functional derangements can in principle be correlated quite well with the renal pathological changes. The glomerular capillary lesion results in the filtration of excessive quantities of albumin and globulin, and in proteinuria accompanied by frank bleeding with hematuria and the formation of red cell casts, even while the overall filtration rate is markedly reduced by thickening of the glomerular membranes and inadequate perfusion of some glomeruli. The resulting reduction in

filtration rate leads to azotemia, the extent of azotemia varying with protein metabolism, diuresis, edema, and other variables influencing the formation and excretion of urea. Glomerular-tubular imbalance leads to retention of salt and water and the formation of edema. Hypoalbuminemia contributes to edema formation in some instances, but Bradley notes the evidence that acute nephritis reflects a widespread capillary disease in which increased capillary permeability probably contributes to edema formation, as attested, for example, by the appearance of facial edema without evidence of significant retention of sodium and water. He also emphasizes that heart failure, which may contribute to generalized edema, may occur in the absence of hypertension, possibly because of specific injury to the myocardium. He presents data on a boy of 17 in whom edema, hematuria, severe flank pain, proteinuria, and azotemia appeared 1 week before the rapid development of cardiac failure (orthopnea, dyspnea, cyanosis, and pulmonary edema) with no great elevation of blood pressure, indicating that the kidneys were the primary source of difficulty, the onset of heart failure only serving to exaggerate the difficulty.

The convulsive seizures and other neurologic disturbances that frequently appear during the course of acute nephritis are believed to arise as a result of hypertensive cerebrovascular disease and resemble the encephalopathic episodes observed in the course of essential hypertension. Whether hemorrhage, vasospasm, edema, or possibly small thromboses are chiefly responsible remains disputed. Bradley notes that the cause of hypertension in acute nephritis remains unexplained, and insufficient evidence is at hand to warrant speculation.

Edema is generally present at some phase of chronic glomerulonephritis, but its appearance is variable and inexplicable. Acute sodium chloride loading in subjects without edema or heart failure does not generally lead to edema. The excretion of potassium is increased, frequently at a rate in excess of filtration.[299]

Hayman, Martin, and Miller [939] made post mortem counts of the number of glomeruli in the kidneys of patients dying with and without renal disease and correlated these with the pre-existing urea and creatinine clearances. In chronic glomerulonephritis and malignant nephrosclerosis the clearances correlated well with

the number of functioning glomeruli. The maximal specific gravity decreased with the decrease in the number of glomeruli until the latter reached 700,000 to 800,000 per kidney, after which it remained fixed in spite of further reduction in the glomerular count.*

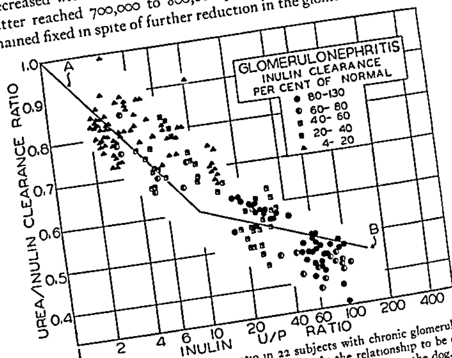


FIGURE 150 Urea/inulin clearance ratio in 22 subjects with chronic glomerulonephritis in relation to the inulin U/P ratio. Line A: the relationship to be expected at urine flows of about 20 cc/min based on observations on the dog.[1853] Line B. the best straight line through normal data (see fig 12). At any inulin U/P ratio, the fraction of urea reabsorbed is essentially the same (or slightly less) in the nephritic kidney at all stages of the disease as it is in the normal, showing that azotemia is due to decreased urea filtration rather than increased reabsorption (Chasis and Smith [363])

Chasis and Smith [363] examined the reabsorption of urea in 22 subjects with chronic glomerulonephritis. As noted elsewhere (ch. IV), urea is invariably reabsorbed from the glomerular filtrate as the urine is increasingly concentrated in the tubules, whether the filtration rate is normal or reduced by disease. The urea/inulin clearance ratio is the only reliable index of the extent of this reabsorption, and because of the variability of urine flow this ratio

* In certain acute infections and jaundice, both clearance and concentrating ability may be markedly reduced in spite of a normal number of glomeruli.

can only be analyzed in terms of the inulin U/P ratio. At any inulin U/P ratio the reabsorption of urea in the nephritic kidney proceeds essentially as it would in the normal kidney, as shown

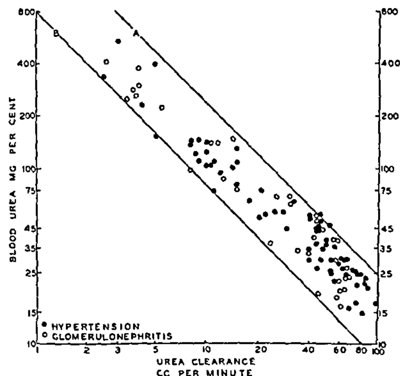


FIGURE 151 Relationship of blood urea concentration to urea clearance (as per cent of normal) in 103 observations in patients with hypertension or glomerulonephritis The urine volume was always above 1 5 cc/min.

On a constant protein diet, elevation of blood urea must begin with the first reduction in the urea clearance. For all points on lines A and B the rate of urea excretion equals 24 and 8 mg/min, respectively, representing the metabolism of 100 8 and 33 6 gm of protein per day (Goldring and Chasis [78])

in figure 150. As concentrating power is lost with advancing disease and the modal inulin U/P ratio decreases, the extent to which urea is reabsorbed decreases so that the urea/inulin clearance ratio approaches 1.0. *There is no evidence of increased back diffusion* of urea (excessively low urea/inulin clearance ratio) in the subjects with chronic glomerulonephritis examined by Chasis and

Smith (no cases of acute nephritis were studied). Excluding the functional change in the urea/inulin clearance ratio which issues from diminishing concentrating power (decreased inulin U/P ratio) as the disease progresses, the elevation of the plasma urea may be viewed as solely a result of the reciprocal relationship (at a constant level of protein metabolism) between the plasma urea concentration and the urea clearance. The relation between the plasma urea concentration and the urea clearance is the simple one that the product of the plasma urea concentration in mg/cc. times the urea clearance in cc/min. must equal the rate of excretion, UV, in mg/min. On a constant protein diet, the last term is itself constant, and hence $P \times UV/P = k$. If P is plotted arithmetically against UV/P a rectangular hyperbola is obtained, or when the two terms are plotted logarithmically, the resulting curve is a straight line, as in figure 151. It is consonant with this interpretation that Govaerts (*Festschrift for Thomas Addis*) [825] has found that the urea/creatinine clearance ratio is maintained within the normal range in chronic nephritis, whereas in mercury, bismuth, uranium, and oxalate intoxication, all of which involve specific tubular injury, this ratio falls to very low values, indicating back diffusion of urea with doubtless complete loss of total urine through more severely injured nephrons.

RENAL RESERVE

The statement is sometimes made that the blood urea concentration rises above normal only after the urea clearance has fallen to 40 per cent of its normal value or below, implying that 60 per cent of the renal parenchyma must be destroyed before there is an abnormal accumulation of urea in the blood. This statement is not only clinically misleading but wholly inaccurate. We cannot speak of any 'renal reserve' in the process of filtration generally or the excretion of urea specifically; so long as nitrogen metabolism * and total body water remain constant and nitrogen equilibrium obtains, the blood urea must vary inversely with the urea clearance from the very first reduction in the latter.[261] The 'normal' whole blood urea nitrogen may be taken as ranging from 5

* The rate of urea production in the dog is markedly increased during hydration, for unexplained reasons [1446]

to 23 mg/100 cc., in the great majority of persons between 8 and 18 mg/100 cc.,[1073, 1597] and, if this fact is ignored, a 100 per cent increase in the level of blood urea will be ignored. In addition, however, variation in nitrogen metabolism and in water intake, the latter operating through changes in urine flow, may cause significant variations in the level of the blood urea independently of the status of the kidneys. It is possible to alter the level of the blood urea substantially by varying the protein intake, the value of the urea clearance remaining unchanged. The average blood urea concentration of 10 medical students on a mixed diet is reported by Addis, Barrett, Poo, and Yuen [17] as 33 mg/100 cc.; on 0.5 gm. of food protein per kg. of body weight per day, the average was 19 mg.; on 1.5 gm of protein 39 mg., and on 2.5 gm. of protein 45 mg/100 cc. Peters and Van Slyke [1597] estimate that in normal subjects the ratio gm. of nitrogen metabolized per day: mg. of urea nitrogen per 100 cc. of blood averages approximately 1:1. The problem is somewhat complicated by the facts that the mean urea clearance over a period of 24 hr. tends to increase up to a certain level with the protein intake (0.3 to 2.4 gm/day per kg) without change in the fraction of urea reabsorbed, that on a high protein diet the urea itself promotes diuresis and reduces reabsorption, and that short-period urea clearances do not exactly reflect 24 hr excretion.[1266] But, in the simplest calculation, if one takes the average protein metabolism as 50 gm/day, the urea production would be 16 gm/day, at an average urea clearance of 50 cc/min (at average urine flows) the plasma urea concentration should average 11 mg/100 cc Reducing the urea clearance by one-half would only double this value. It is obviously impossible, in view of variations in protein metabolism and diuresis, to detect a 50 per cent reduction in renal function by the increase in plasma (or whole blood) urea concentration Goldring and Chasis [795] have shown that the blood urea can be elevated from 52 to 276 mg/100 cc. by varying the protein intake from 13 to 238 gm/day. Children particularly frequently have disturbances (anorexia, vomiting, and diarrhea) which markedly influence urea production, filtration rate, and urine flow, and it may be expected that the level of blood urea will for these reasons alone show such variations as

will obscure the true inverse relation between the blood urea and the urea clearance.

UREMIA

Terminally, concentrating power is lost and the specific gravity of the urine becomes fixed between 1.008 and 1.012. All clearances are reduced, leading to azotemia. Death, if not caused by intercurrent infection or other extrarenal disturbance, occurs from severe imbalance in the composition of the body fluids (edema, acidosis, hyponatremia, hypokalemia, hyperphosphotemia, etc.) complicated by anemia, circulatory disturbances, and other factors of unknown nature. Correction of anemia does not lessen or increase the severity of uremic manifestations or influence the progress of the disease.[602]

The terminal state in renal failure is known as uremia, an expression historically derived from the early recognition of elevated blood urea concentration. The retention of urea itself, however, does not account for the toxic manifestations and physiological disturbances of renal failure, and the actual cause of death must be conceived as complex and possibly representing the summated action of numerous physiological disturbances, no one of which may be lethal in itself and no one of which is consistently predominant in the uremic state.[225 227,1477] In a lesser proportion of cases, heart failure, cerebral hemorrhage, or cerebral thrombosis issuing as sequelae from persistent hypertension and arteriolar disease may be the immediate cause of death.

Winkler, Hoff, and Smith[1021,2237] have shown that, in animals rendered anuric by nephrectomy or ureteral ligation, death regularly results from the extracellular accumulation of potassium to levels that are cardiotoxic. With marked reduction in the filtration rate, the potassium clearance may be inadequate to balance the intake and the plasma level may rise to abnormal values such as threaten the life of the patient. Death in man may occur, however, in the presence of a normal or low plasma concentration of potassium and be due to causes quite unrelated to disturbances of potassium metabolism. Nevertheless the administration of potassium is contraindicated in any patient with anuria or oliguria.[595,1099]

Earle (pers. com.) finds that the potassium concentration tends

to increase in both acute and chronic glomerulonephritis when the filtration rate falls below 50 cc. In 45 observations on 21 patients, the plasma potassium concentration was above normal (i e. above 5.1 mEq/liter, a value 2σ above the mean normal of 4.4) in 18 out of 29 observations made when the filtration rate was below 50 cc., while 2 were below normal (3.7 mEq/liter). In no case was the potassium concentration high enough to be of serious consequence, the highest figure being 6.7 mEq/liter; however, only 5 of the observations could be classified as being made in the terminal phase (filtration rate below 10 cc.). Whereas normal subjects on normal potassium intakes excrete less than 20 per cent of the filtered potassium load, in 22 of the 29 observations cited this figure exceeded 20 per cent. Excretion exceeded filtered load (indicating tubular excretion) in 2 patients, one of whom was in the terminal phase. The other patient, however, was unique in that he suffered from hypokalemia owing to a defect in the renal tubules. Tubular excretion could readily be demonstrated in this patient when the filtration rate was as high as 70 cc.

Leaf and Camara [1219] report that in 24 hr. clearances in 4 patients with advanced nephritis, the potassium/endogenous creatinine clearance ratio averaged 1.41 in 8 observations, with a range from 1.21 to 1.64. In one of these subjects, maintained on a diet containing 68 mEq/day of potassium, this clearance ratio averaged 1.91 in 8 observations, with a range of 1.78 to 2.01. (Carinamide was without effect on the clearance ratio.) Had potassium excretion been limited to that which was filtered only, the subject would have been retaining nearly 30 mEq/day and could not have survived long. Thus the authors conclude that, whatever the mechanism of predominance of potassium tubular excretion over reabsorption in advanced renal disease, it is important in preventing potassium intoxication and may even reduce the plasma concentration to subnormal levels.

PROTEINURIA IN NEPHRITIS

The appearance of protein in the urine is characteristic, though not invariable, in glomerulonephritis. That the urinary protein is derived from plasma protein by filtration has been established by studies on protein excretion in the normal kidney (ch. 3 [illegible])

question remains to be answered how much protein is normally filtered and reabsorbed and to what extent filtration is increased in renal disease. It is improbable, however, that proteinuria is ever attributable solely to decreased tubular reabsorption.

Jens Bing,[167] from his own studies and those of others, concluded that total protein and albumin excretion in a particular subject examined over a short time varied proportionally with the creatinine clearance (and in general with the urea clearance),* while the protein concentration in the urine varies with the creatinine U/P ratio, these relations being unaffected by water diuresis, urea diuresis, or pitressin antidiuresis. It is therefore irrational to report proteinuria in terms of urine concentration, the only meaningful figure being the rate of excretion, UV, and the most valuable datum, of course, the 24 hr. excretion. Albumin predominates in the urine, but changes in the albumin/globulin ratio of the plasma are reflected by similar changes in the urine, though the relative quantities of these proteins in the urine vary widely from patient to patient. Protein excretion is generally greater during the day than the night. Total protein excretion in any one subject tends to parallel the filtration rate and plasma protein concentration, but it is increased on a high protein diet and decreased on a low protein diet without changes in filtration rate, the factors underlying this relationship being obscure.[14, 128, 1594]

Many clinical studies afford information on the relationship of proteinuria to the life history of renal disease,[14, 127, 524, 653, 1115, 1597, 1762] but as yet they have failed to clarify the relative importance of filtration and tubular reabsorption.

THE NEPHROTIC SYNDROME (NEPHROSIS)

The nephrotic syndrome designates the occurrence (most importantly in children in the age group of 1 to 6 years) of gross edema, *proteinuria, and hypoalbuminemia, usually with hypercholesterolemia* and lipemia, frequently appearing in the absence of hypertension and hematuria.[115, 244, 1028, 1818] The syndrome accompanies *renal amyloidosis*, intercapillary glomerulosclerosis, disseminated lupus erythematosus, occasionally the course of syphilis and renal

* The excretion of cholesterol in cholesteroluria also parallels these clearances.

vein thrombosis. It does not occur in other renal involvements such as pyelonephritis, arteriolar nephrosclerosis, or essential hypertension, this negative fact having some significance with respect to etiology. In the absence of a specific diagnosis, it is considered by some investigators to be a distinct disease entity, pure, genuine, or lipoid nephrosis, those who hold this view accept that glomerulonephritis (hematuria, hypertension, and azotemia) may be superimposed upon pure nephrosis or that the nephrotic syndrome may terminally result in a state of renal insufficiency clinically and pathologically indistinguishable from chronic glomerulonephritis. In this view, differentiation between the nephrotic syndrome and the nephrosis of amyloid disease, intercapillary glomerulosclerosis, lupus erythematosus, etc. (diseases occurring in adulthood and not in the first decade), must depend on basic diagnosis. Others believe that nephrosis is but one aspect or phase of glomerulonephritis, and that failure to identify it as such is attributable to the absence of evidence of antecedent infection or the absence of clinical evidence of the initial attack of acute glomerulonephritis. In the latter view, the nephrotic syndrome may follow directly upon acute glomerulonephritis or after a latent asymptomatic period; or acute glomerulonephritis may go unrecognized and the nephrotic syndrome may suddenly appear in an otherwise well child.

In severity the nephrotic syndrome may vary from a benign affliction to one in which there is severe anorexia and diarrhea, acute or chronic infection and incapacitating anasarca, with protein excretion amounting to 10 to 20 gm/day usually accompanied by abundant protein casts Patients with the nephrotic syndrome may develop renal insufficiency insidiously or after the frank nephritic manifestations of hematuria and hypertension, and die of infection or renal failure. In a significant number, however, and particularly in children, the disease runs a course of a few months to 5 years, marked by spontaneous remissions, and is self-limited. A second episode, once recovery is effected, is not authenticated.

In the absence of renal insufficiency, the pathological changes in the kidney may be so slight as to escape definition: diffuse thickening of the basement membrane in the glomeruli with multiplication of the mesangium is perhaps the most basic change. Pathological interpretation is complicated by the circumstance

that milder cases are not fatal. In more severe cases, the most characteristic feature is marked swelling of the cells of the proximal tubule (perhaps a physiological reaction to the extensive reabsorption of protein which passes into the urine as a result of increased glomerular permeability) and accumulation of excessive quantities of fat in the form of doubly refractile droplets in these cells, this latter circumstance giving the syndrome the name of lipoid nephrosis. This fat accumulation appears to result from deranged metabolism rather than tubular reabsorption, since there are no free lipids excreted in the urine.* [115]

Since hypoproteinemia is characteristic of the nephrotic syndrome, it is of interest that O'Leary and Corson [1643] found that reduction of plasma proteins from 6.1 to 3.3 gm/100 cc. in dogs by a low protein diet and repeated plasmapheresis had little effect on the filtration rate or renal plasma flow.† The filtration fraction decreased slightly (from 0.33 to 0.28). It seems to be generally true that changes in oncotic pressure, like changes in arterial pressure, are not directly reflected in changes in renal function because they are wholly offset by autonomous changes in the renal circulation, or by changes in the latter brought about by factors the nature of which remains unknown.

Such unknown factors are clearly operating on the renal circulation in nephrosis, because a notable feature of renal function in nephrotic children is a tendency to increased glomerular activity. Farr [623] found that the urea clearance possesses a degree of lability far exceeding that observed in normal adults, or in children or adults with decreased urea clearances. Protein intakes of 0.5, 1, 2, 3, and 4 gm/kg per day were accompanied by average urea clearances of 73, 88, 178, 184, and 216 per cent of the mean normal value. The creatinine clearances varied in a similar manner.

* Olive oil and bone marrow fat may be excreted in the urine of dogs and guinea pigs after intravenous administration, but the role of embolic injury is not ruled out [1815, 2300] In general there is no evidence that lipids pass in any significant quantity through the glomeruli or are excreted by the tubules

† It must be noted, however, that a symmetrical reduction in plasma proteins is not equivalent to the excessive reduction in albumin concentration which occurs in the nephrotic syndrome, where the latter may be decreased to 0.4 gm/100 cc This is particularly important since albumin has about 4 times the oncotic pressure of globulin per gm. of protein.

ner. Urea was without effect. This lability is less frequently observed in nephrotic adults or children over 10 years of age. Emerson, Futcher, and Farr [605] found that the urea clearance is frequently increased for periods of one or more months to 140 per cent or more of the normal, and in one child observed by them it was consistently elevated to between 200 and 300 per cent of normal for 6 years. They found that the inulin clearance is elevated as much as or more than the urea clearance, the urea/inulin clearance ratio remaining within the normal range in most observations.* The intravenous administration of casein hydrolysate to patients with low clearances did not increase the filtration rate.

The creatinine/inulin clearance ratio in 3 children with high inulin clearances (193, 171, and 233 cc.) averaged 1.55, 1.76, and 1.33; in 2 recovered children with normal inulin clearances (117 and 151 cc.) this ratio was 1.50 and 1.22; in 3 children with low inulin clearances (13.8, 12.3, and 17.4 cc.) the ratio was 1.20, 1.32, and 1.16. The endogenous creatinine chromogen/inulin clearance varied widely below and above 1.0, but the data are complicated by an uncertain correction for non-creatinine chromogen in the Folin creatinine method.

Emerson and Dole [602] report that in 4 nephrotic children the elevated filtration rate is accompanied by increased renal blood flow. The average diodrast clearances were 766, 622, 1046 (1232 on the same subject on another occasion), and 884 cc. The corresponding inulin clearances were 178, 200, 216 (270), and 197. The data leave no question that, in the hyperfunctional stage, both renal blood flow and filtration rate may be increased to an extent not observed in other clinical conditions and which cannot be achieved by the administration of any known agents.† The urea/inulin clearance ratios do not appear to be unusual.

Supernormal filtration rates are also reported by Galán [734] in some children with nephrosis, though the average figure, 133

* Despite a marked tendency to increased filtration rate, it must be emphasized that in general renal function is reduced in nephrotic children in much the same manner as in chronic glomerulonephritis

† The filtration rate does not increase in this manner in pyrexial hyperemia. Equivalent but transient increases in renal blood flow are, however, immediately induced by the intravenous administration of concentrated human plasma albumin

$\pm$ 47.3 cc.,* is identical with *that writer's normal series* (*133* $\pm$ 14.9 cc.). The average diodrast clearance was slightly greater than normal (793 $\pm$ 183 as compared with 695 $\pm$ 183 cc.), the filtration fraction slightly lower (0.17 $\pm$ 0.06 as compared with 0.19 $\pm$ 0.02). Tm_D averaged 57.3 $\pm$ 17 (normal 53 $\pm$ 11 mg. of iodine). It is of interest that Tm_G, which Galán and his coworkers [735] have shown to be supernormal in children (on a surface area basis), has a slightly greater value in nephrosis, 577 $\pm$ 164 mg. (normal 543 $\pm$ 129). C_D/Tm_D averaged 14.06 $\pm$ 2.18 (normal 15.26 $\pm$ 6.4), C_{IN}/Tm_D 2.63 $\pm$ 0.7 (normal 3.01 $\pm$ 0.64), C_{IN}/Tm_G 0.201 (normal 0.395). There were no significant differences in these figures when edema was present or absent. The author emphasizes his view that increased reabsorption of sodium is important in the genesis of nephrotic edema,† and contrasts the maintained or elevated filtration rate with the reduced rate observed by him and others in chronic nephritis.

Luetscher [1281] reported a single patient in whom the intravenous injection of 25 gm. of human plasma albumin increased the mannitol clearance from 101 to 177 cc. The albumin clearance increased proportionally (0.39 to 0.66 cc.), and in other observations the 24 hr. clearance remained constant, irrespective of plasma albumin level.

The decreased colloid osmotic activity of the plasma may facilitate the development of edema but is not the sole factor determining *the presence or absence of clinical edema. Luetscher* [1282] has found that the repeated administration of concentrated human serum albumin to patients with nephrosis increases the concentration of albumin and the oncotic pressure of the plasma, but the measure is frequently ineffective in increasing the excretion of salt and water. Spontaneous diuresis differs from the diuresis induced by the administration of albumin in that the plasma volume and protein concentration may change only slightly during spontaneous diuresis, *while the proportion of sodium reabsorbed* is

* It may be repeated that average figures in renal disease have little mean- [illegible] periods from su-

[illegible] veals only that

[illegible] chloride excretion is reduced

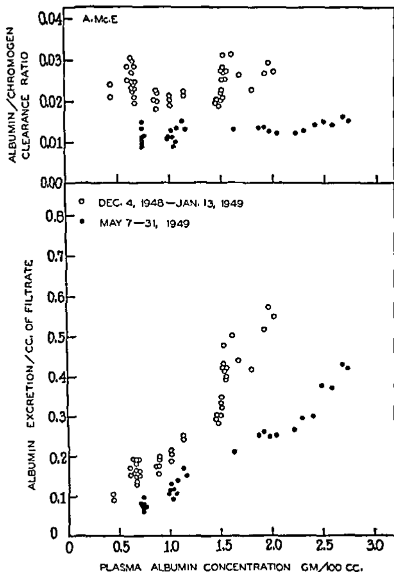


FIGURE 152 The relationship between plasma albumin concentration and (above) the albumin/endogenous creatinine chromogen clearance ratio and (below) albumin excretion in a 5-year-old nephrotic child.

The first clearance period (highest P_{ALB}) began at 6 A M on the day after the last dose of albumin (37 5 gm) By this time most of the disturbing effect

diminished even more than after albumin therapy. Luetscher concluded that excessive reabsorption of sodium is independent of the total circulating protein.

Under acute sodium loading, nephrotic subjects with normal or only moderately reduced filtration rates respond with poor sodium excretion, sodium and water continuing to be reabsorbed to exaggerate the edema.[299]

Eder, Chinard, Grief, Cotzias, Hiller, Van Slyke, and Lauson (pers. com.)[668, 669] have utilized the endogenous creatinine chromogen clearance to follow selected patients on an around-the-clock basis, repeating their studies during edema formation, during spontaneous or albumin-induced diuresis, and in an after-period of either edema reaccumulation or sustained well-being. From these studies they visualize the sequence of events as follows: albuminuria leads to hypoalbuminemia and a reduction in plasma and blood volume; hypovolemia in turn leads to renal ischemia and decreased filtration rate, which in turn leads to excessive conservation of sodium chloride (and water) and to edema formation. Where edema occurs in the presence of normal or increased filtration rate, they believe that there may be a corresponding increase in tubular activity. The possible role of increased adrenal cortical activity and of antidiuretic substances from the pituitary (ADH) or liver (VDM) is considered but left an open question.

The clearance of albumin in one subject was found to be essentially constant at about 1 cc., and independent of plasma concentration when this decreased slowly from 2.5 to 0.4 gm/100 cc. during 3 weeks after cessation of albumin therapy (fig. 152). The albumin/endogenous creatinine chromogen clearance ratio re-

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of the acute increase in plasma volume had passed In the first study (circles), 2 complete round-the-clock days were measured, and on 4 other days morning periods only were obtained These correspond to plasma albumin concentrations of 0.4, 0 65, 1.0, and 1.15 gm/100 cc. In the second study (dots), the patient had improved clinically. Three round-the-clock studies were obtained at this time.

The data indicate, first, that the albumin clearance is independent of the plasma albumin concentration and hence $U_{ALB}V$ increases in proportion to P_{ALB}. Second, the permeability of the glomerular membranes was reduced about half in association with clinical improvement between December 1948 and May 1949. (Eder, Chinard, Grief, Cotzias, Hiller, Van Slyke, and Lauson, pers com.[669])

mained in the range of 0.025 to 0.030. Repetition of this study in the same patient 5 months later, when she had improved clinically, gave the same relationship, with an average albumin/chromogen clearance ratio of 0.012. Data in 4 additional patients were consistent in this respect. Since there was no tendency for the albumin clearance to decrease at even the lowest plasma concentration, albumin excretion does not appear to issue from the circumstance that the filtered load exceeds a limited reabsorptive capacity, or, if there is a limited reabsorptive capacity, it is small in comparison with the filtered load.

The authors believe that an increase in the permeability of the glomerular membrane is responsible for proteinuria. When the plasma albumin concentration was raised to 1.94 gm/100 cc. in a nephrotic child, the concentration in the glomerular filtrate (assuming no tubular excretion) must have been at least 125 mg/100 cc., as calculated from albumin excretion in mg/min. divided by the inulin clearance By proportion, this would mean the presence of 260 mg/100 cc of albumin in the glomerular filtrate at normal plasma albumin concentrations Similar calculations in other cases give values of the order of 115 to 305 mg/100 cc., all values much higher than those found by direct analysis of normal glomerular fluid in mammals The magnitude of albumin excretion seems therefore to be related to the filtration rate In some instances, for several hours following the infusion of albumin, the albumin clearance increased more than did the filtration rate. This phenomenon was correlated with an acute expansion of plasma volume, and may represent a phase of increased glomerular permeability induced by albumin administration

With the decrease in plasma albumin concentration consequent to proteinuria, water and other solutes move from the plasma to the interstitial compartment, leading to a reduction in plasma and blood volume. Serial measurements indicate that reductions of 20 to 30 per cent in plasma volume may occur during edema accumulation. When the plasma volume decreases rapidly as a result of a spontaneous, sudden increase in proteinuria, symptoms of mild circulatory insufficiency, such as faintness, sweating, and thirst, may appear, particularly in the upright posture.

Reduction in plasma volume was usually accompanied by a

decrease in renal plasma flow and filtration rate and in the excre-
tion of salt and water. Where the reduced plasma volume was re-
expanded by administration of albumin, moderate increases in

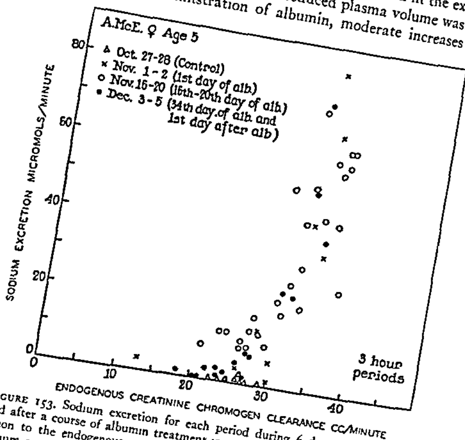


FIGURE 153. Sodium excretion for each period during 6 days before, during and after a course of albumin treatment in a 5-year-old nephrotic child, in relation to the endogenous creatinine chromogen clearance. It is obvious tl sodium excretion stops at a critical chromogen clearance of about 25 cc/m (Eder, Chinard, Grief, Cotzias, Hiller, Van Slyke, and Lauson, pers. com.[199])

the filtration rate occurred in most instances. Analysis of many periods showed a good correlation between the increased excretion of salt and water and the increased filtration rate (fig. 153), and failure to achieve diuresis and chloruresis following albumin administration correlated with failure to raise the filtration rate in spite of plasma volume expansion. It was only after edema had completely disappeared as a result of albumin therapy that significant exceptions were noted; then moderate increases in plasma

volume and filtration rate following albumin infusion sometimes failed to be accompanied by an increase in salt and water excretion. It may be noted that albumin administration in normal subjects may have little effect on the filtration rate and may decrease sodium excretion.[112]

Despite the general correlation between filtration rate and sodium excretion, edema may occur in nephrotic patients who have a normal or even supernormal filtration rate. Eder *et al.* believe that this circumstance is related to supernormal reabsorption capacity on the part of the tubules. There is no way at the present time to evaluate tubular function with respect to sodium reabsorption in man, but that tubular function may be increased in such patients with supernormal filtration rates is indicated by the fact that, in a few instances examined, Tm_{PAH} and Tm_G were elevated more than were the filtration rate and PAH clearance, leading to low functional ratios, in 3 patients, C_{PAH}/Tm_{PAH} was 5.93, 3.56, and 7.06 (normal 9.18); C_F/Tm_{PAH} was 0.856, 0.945, and 1.17 (normal 1 72). It may be noted that Eder *et al.* confirm the supernormal values of Tm_G reported by Galán [114] in nephrotic children; in the two instances examined they report Tm_G to be 679 and 603 mg (normal adult male figure 375 ± 79.7 mg.) and C_{IN}/Tm_G to be 0.187 and 0.257 (normal 0.371 ± 0.05).

Whether the excessive filtration and reabsorption of protein in the nephrotic syndrome injures the renal tubules remains a moot question [12] However, Eder *et al* observed one 19 year old girl in whom renal function completely recovered after 6 weeks of daily albumin administration. She excreted about 50 gm/day for over 3 weeks, and some urine specimens contained over 10 gm/100 cc.

Metcoff, Kelsey, and Janeway (pers com.), from studies of 25 children 15 months to 14 years of age, arrive at the tentative belief that the several forms of the nephrotic syndrome may be interpreted physiologically as three successive phases of a single diffuse renal disease. The initial phase, lasting 1 to 2 months, is characterized by decreased filtration rate, normal or increased renal plasma flow and Tm_{PAH}, and decreased filtration fraction. Clinically, the acute onset of this phase without hematuria, hypertension, or azotemia has been designated 'acute nephrosis,' whereas if microscopic hematuria or slight azotemia is initially

present the clinical diagnosis may be 'tubular' or 'mixed' nephriti Usually the initial stage is followed by a second phase, lastin several months, in which the filtration rate may be increased o decreased. If there is a supernormal filtration rate or urea clearance, minimal or absent hematuria, and no azotemia, a diagnosis of 'true' or 'lipoid' nephrosis may be made; if hematuria and slight azotemia persist in the presence of a reduced filtration rate and urea clearance, the clinical classification may be 'subacute glomerulonephritis.' Physiologic and clinical recovery may follow. If recovery does not occur, progressively decreasing renal function ushers in the last phase, which is associated with the obvious evidences of severe renal damage, including acidosis, anemia, continued hematuria, azotemia, and hypertension, signs which would be considered as manifestations of the 'nephrotic syndrome of chronic glomerulonephritis' or 'degenerative nephritis.' According to these workers, the extent and type of functional impairment is determined by the severity of renal response and duration of the disease, rather than the age at or mode of onset.

Shorr, Zweifach, Mazur, and Payne (pers. com.) report that VDM is greatly increased in the peripheral blood in the nephrotic syndrome of glomerulonephritis (as well as in decompensated hepatic cirrhosis with edema and ascites and in congestive heart failure with edema). VDM was also increased in all the edema fluids. In these instances the concentration of VEM is not increased.

The dietary restriction of salt remains the most effective means of controlling the edema of renal origin, though recent studies indicate that diuresis may occur following the oral administration of sodium lactate, sodium acetate, or potassium acetate.

The intravenous administration of salt-poor human serum albumin produces temporary diuresis in about one-half of patients in the nephrotic phase, but this does not seem to influence the course of the disease.

Gum acacia has been shown to be an effective diuretic agent in the edematous state, but prolonged hepatic retention of this compound and signs of toxic action contraindicate its use.[1818]

It is of particular interest that induced measles may produce a prolonged remission with complete diuresis and disappearance of proteinuria in patients with lipoid nephrosis or in the nephrotic

stage of chronic glomerulonephritis, confirming a long record of remissions observed during accidental infection.[155, 1069, 1429, 1743] Chasis, Goldring, and Baldwin[383] have found that therapeutic doses of HN_2 reduced proteinuria in 3 patients in the nephrotic stage of chronic glomerulonephritis and produced diuresis in 1, with unchanged or increased filtration rate, indicating that temporary reversal of the renal manifestations of human glomerulonephritis can be induced by this compound. The mechanism of the action of HN_2 is unknown.

MASUGI NEPHRITIS

As first shown by Lindeman (1900), Pierce (1903), and Masugi (1912), the intravenous injection into rats, rabbits, and other mammals of antiserum prepared from homologous kidney may incite acute and sometimes progressive renal lesions resembling glomerulonephritis. The antigen is apparently glomerular in origin, whereas all other cortical components are antigenically inert.[886] A similar reaction follows the injection into rats of rabbit anti-rat placenta serum, and the injection of heminephrectomized rabbits with purified bovine serum gamma globulin. To what extent Masugi or nephrogenic nephritis bears upon the origin of acute or glomerulonephritis is undetermined.[1140, 1474, 1817, 1963]

Fouts, Corcoran, and Page[892] prepared an anti-dog kidney serum by the injection of sterile emulsions of dog kidney into chickens. Injection of such sera into dogs, after a latent period of 6 to 10 days, produced hematuria and proteinuria. One or two days before proteinuria reached its peak, the phenol red clearance was at or above control levels, while the inulin clearance was depressed. The inulin clearance continued to decrease during the next 6 to 12 days, and terminally the phenol red clearance also decreased. EPR was decreased at the peak of the reaction, but the creatinine/inulin clearance ratio did not fall below 1.0. The authors conclude that, early in the nephrotoxic response, renal hyperemia occurs, accompanied by thickening of the glomerular membranes; as glomerular swelling increases, the capillaries become occluded so that the renal blood flow decreases. Hematuria occurs at the onset of the reaction, but is apparently not related to hemolytic or anaphylactic reactions that follow the injection of

sera. The course of the anemia subsequent to the early hemolytic reaction suggests depression of bone marrow activity.

Moses and Thornton [1480] prepared nephrotoxic sera in rabbits by the intraperitoneal injection of minced dog kidney. On administration of such sera to normal dogs, after a latent period of 6 to 12 days, there followed a consistent decrease in urea and creatinine clearances with only minor variations in renal blood flow. There was complete loss of tubular capacity to excrete PAH, and in several instances PAH excretion fell below the rate of its filtration, indicating back diffusion. Biopsy specimens revealed only moderate glomerular and tubular damage.

HYPOSTHENURIA AND ISOSTHENURIA

Impairment or loss of concentrating power is encountered in a variety of conditions such as acute and chronic glomerulonephritis, arteriolar nephrosclerosis, chemical poisoning, prostatic obstruction, pyelonephritis, polycystic kidney, renal trauma, severe anemia, periarteritis nodosa, lupus erythematosus, etc. Consequently, the specific gravity of the urine under standard conditions of dehydration is a useful if nonspecific test for renal damage. It is probable that the hyposthenuria of chronic glomerulonephritis and malignant nephrosclerosis, where functional renal tissue is greatly reduced, has a different physiological basis than that observed in conditions in which renal function is disturbed but severe renal injury has not occurred. Complete loss of concentrating power in renal disease represents in general an advanced and irreversible destruction of a large proportion of nephrons, whereas in other conditions it may represent only a reversible functional disturbance.

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Hayman, Shumway, Dumke, and Miller[641] examined the increased glomerular filtrate hypothesis by observing the consequences of subtotal nephrectomy in dogs, an operation which leads to polyuria and hyposthenuria in this and other species.[316] Approximately one-third of the right kidney was excised, and 2 to 6 weeks later the left kidney was removed. With other investigators, they found that the urine volume during concentration tests was increased 2- to 5-fold and concentrating power was lost, the maximal specific gravity being reduced to 1.014 to 1.028 as compared with control values of 1.030 to 1.052. Pituitrin plus water deprivation did not increase the specific gravity above the value reached during water deprivation alone. Adrenal cortical hormone also was without effect. The inulin, creatinine, and urea clearances were reduced to one-half to one-tenth of normal, the creatinine/inulin clearance ratio in 2 dogs remaining at 1.0. The capacity to excrete a dilute urine (specific gravity less than 1.002) was not impaired. The increase in filtration rate, characteristic of normal dogs on a high protein diet, seemed to be nearly abolished, but one dog, which did double its filtration rate on a meat plus sodium chloride diet, concentrated to 1.029 as compared with 1.022 on a cracker meal diet, arguing against excessive filtration being the cause of hyposthenuria.

More significantly, the elevation of the plasma oncotic pressure by acacia, infusion of concentrated plasma, or dehydration of the animal by various means produced in general as concentrated or more concentrated urine than had been formed before operation

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Late in the course of renal disease and frequently dissociable from the appearance of hyposthenuria, the capacity of the kidney to elaborate a dilute urine is lost and the specific gravity becomes fixed in the range 1.010 (isosthenuria), i.e. equivalent to that of the glomerular filtrate or slightly higher because of albuminuria.

Numerous theories have been advanced to explain the hyposthenuria and isosthenuria of renal disease.[941] Fremont-Smith and his coworkers [695] first suggested that with progressive renal disease a large volume of filtrate is formed in a small number of glomeruli,

thus leading to flooding of the tubules. In current terms, this would be equivalent to osmotic diuresis effected by an increased load of filtered sodium chloride, resulting in overloading of the distal tubule with respect to both sodium and water and a consequent reduction in the osmotic pressure of the urine. However, one might expect *a priori* that the distal reabsorption of both sodium and water, because they involve osmotic work, would be very sensitive to anoxic or other injury. The fact that concentrating power is lost in so many circumstances suggests that the distal reabsorption of water is more readily impaired, and that only later, when isosthenuria has developed, is distal reabsorption of sodium markedly reduced.

Hayman, Shumway, Dumke, and Miller [951] examined the increased glomerular filtrate hypothesis by observing the consequences of subtotal nephrectomy in dogs, an operation which leads to polyuria and hyposthenuria in this and other species.[448] Approximately one-third of the right kidney was excised, and 2 to 6 weeks later the left kidney was removed. With other investigators, they found that the urine volume during concentration tests was increased 2- to 5-fold and concentrating power was lost, the maximal specific gravity being reduced to 1.014 to 1.028 as compared with control values of 1.030 to 1.052. Pituitrin plus water deprivation did not increase the specific gravity above the value reached during water deprivation alone Adrenal cortical hormone also was without effect The inulin, creatinine, and urea clearances were reduced to one-half to one-tenth of normal, the creatinine/inulin clearance ratio in 2 dogs remaining at 1.0 The capacity to excrete a dilute urine (specific gravity less than 1.002) was not impaired. The increase in filtration rate, characteristic of normal dogs on a high protein diet, seemed to be nearly abolished, but one dog, which did double its filtration rate on a meat plus sodium chloride diet, concentrated to 1.029 as compared with 1.022 on a cracker meal diet, arguing against excessive filtration being the cause of hyposthenuria

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More significantly, the elevation of the plasma oncotic pressure by acacia, infusion of concentrated plasma, or dehydration of the animal by various means produced in general as concentrated or more concentrated urine than had been formed before operation

during water deprivation.* Similarly, the specific gravity of the urine excreted during a period of low blood pressure exceeded the maximal postoperative value and in 2 animals was as high as the mean preoperative concentration test.

The reduction in the creatinine clearance was less than the reduction in the number of glomeruli (glomerular counts were made by a standard technique); reduction of glomeruli to 10 per cent reduced the clearance to only 24 per cent. Thus, with a small residue of renal tissue, activity in residual glomeruli was substantially increased; in view of the evidence that there are no inactive glomeruli in the dog kidney, this must reflect general vascular dilatation. The urea clearance was reduced somewhat less than the creatinine clearance, probably because of diuresis in the residual nephrons and a lower U/P ratio.

Hayman and his coworkers conclude that the hyposthenuria which follows subtotal nephrectomy is not attributable to abnormality of the renal tubules, since under appropriate conditions the animals could concentrate as well or better than before operation. They lean to the interpretation that increased filtration leads to a more rapid flow of fluid down the tubule and that lack of time for reabsorption leads to hyposthenuria. It may be noted that the conditions that led to maximally concentrated urine (acacia, dehydration with croton oil, etc.) may, like reduced blood pressure, have reduced the filtration rate, which unfortunately was not measured under these particular conditions. If such were the case, the experiments would seem to support the glomerular-tubular imbalance theory proposed by Fremont-Smith *et al.* However, it does not seem probable that the velocity of flow (i.e. the time factor) is the important consideration even under these conditions, since the concentration of water (the substance being reabsorbed) remains practically unchanged at low and high urine flows. Overloading of the distal tubules with isotonic proximal urine, as suggested above, would seem to present a more likely explanation. But against this interpretation is the fact that a

* The rise in specific gravity after the intravenous administration of hyper-

doubling of the filtration rate, as between a cracker meal and a meat or meat plus salt diet, did not decrease the maximal specific gravity. It must be said, therefore, that the cause of hyposthenuria in subtotal nephrectomy remains unsolved. In any case it does not follow that hyposthenuria in renal disease has the same explanation as in subtotal nephrectomy, since numerous physiological variables are involved.

Hayman *et al.* show that concentrating power in dogs is not impaired during Goldblatt hypertension or during vitamin B_6 deficiency (black tongue).

The administration of pituitary extracts or pitressin tannate suspended in peanut oil has been frequently recommended to increase the maximal concentration of the urine in short-period concentration tests of renal function;[1035 1569 1578 1795 1959 2054] but Taylor, Peirce, and Page[2054] find that the maximal specific gravity reached in such tests is less than that reached in 24 hr. without fluids (as in the Addis test), and they conclude that there is no entirely acceptable substitute for the latter Horne and Morris[1035] believe that the use of pituitary extract is reliable in selected cases and superior to the Addis test in patients with edema Concentrating power is retained when the filtration rate is reduced in chronic congestive heart failure, and it is apparently not affected specifically by circulatory failure unless renal anoxia supervenes.

SYPHILITIC NEPHROSIS

Furman, Gale, Ory, and Weinstein (pers. com) report on a single subject with syphilitic nephrosis On first examination the inulin and PAH clearances were 76.1 and 456 cc , and Tm_{PAH} 49 8 mg. At the time of study the patient was edematous but there was no oliguria. Heavy albuminuria was present, with numerous fine granular and red cell casts After 2 weeks of treatment with penicillin, these values were 106 5, 525, and 77, and after 7 weeks, 121, 498, and 67.7. Twenty-two days after antiluetic treatment was initiated he had lost 13 pounds of edema fluid and albuminuria had disappeared. The authors liken the renal syndrome to acute glomerulonephritis, in which the filtration rate and Tm_{PAH} are reduced, with a variable blood flow to the residual functional tissue. The condition is so rare,[990] however, that other investigators

believe it is acute nephritis coincident with syphilis and wholly unrelated to the latter.

CHRONIC PYELONEPHRITIS

Pyelonephritis is a renal inflammation of bacterial origin (usually B. coli and staphylococci) arising from infection of the mucous membranes of the pelvis with invasion of the interstitial tissue, and leading, after recurrent acute attacks, to cicatricial contraction of the kidney and widespread or total destruction of the parenchyma. Such infection may be associated with ptosis, calculi, hydronephrosis, prostatism, or obstructive anomalies of the urinary tract; it may arise *de novo* from ascending infection, though Longcope [1264] has presented evidence that the renal infection is generally blood-borne and gains access to the body by way of the gastrointestinal tract. Chronic atrophic pyelonephritis occurs with equal frequency unilaterally and bilaterally, although bilateral involvement is more frequent among females, unilateral among males. There is no predilection for the right or left kidney. The extent to which primary acute attacks may heal completely or progress into the chronic degenerative form remains a matter of debate. In about one-third of the cases uremia is the cause of death, intercurrent infection and unrelated disease account for a large fraction, and in about one-sixth death is a sequel to hypertension. Chronic atrophic pyelonephritis in one kidney is the one renal disease in which the incidence of hypertension is high enough to suggest a causal connection.[1933] It is frequently accompanied by calculi, the formation of which may be secondary to the infection and impaired renal function.

Whether or not the disease arises as a result of ascending infection, it occurs earliest and most severely in the medulla, where inflammatory changes and scar formation lead to compression and destruction of the thin segment and the collecting ducts. These obstructive lesions react upon the cortex, leading to dilation of the proximal tubule and the formation of small cysts. The tubule undergoes atrophy and the lumen is frequently obstructed by casts. Invasion of the interstitial tissue of the cortex leads to wedge-shaped invasive scarring between areas of relatively normal or even hypertrophic tubular tissue. In the scarred areas of

the cortex, the glomeruli of the obstructed tubules tend to undergo hyalinization, and more characteristically the outer layer of Bowman's capsule becomes replaced by a fibrotic ring (periglomerular fibrosis) which encircles a normal capsular space and glomerular tuft. Glomerular degeneration is, however, late, and cases are on record of patients dying in uremia although nearly all the glomeruli were histologically well preserved. Hyalinization of the glomeruli may issue from compression of the afferent and efferent arteriole by the periglomerular fibrotic capsule, by endarteritis obliterans, or by adhesions between the glomerular capillaries and the fibrotic capsule. Even in the acute stage the renal capsule is the seat of local inflammatory reactions (perinephritis) which lead to scarring and adhesion to the cortex

Typically, proteinuria is minimal (0.1 to 1.5 gm/day) and occasionally it is absent even in patients dying in uremia, and protein casts are correspondingly rare Pyuria and bacteriuria (usually B. coli) are usually present, as is hematuria which may result from hemorrhagic pyelitis or cystitis In advanced bilateral disease, concentrating power is lost. The reaction of the urine is acid in B. coli infections but alkaline where the staphylococcus or B proteus is involved, the last two organisms split urea into ammonia and the resulting alkalinization of the urine contributes to the formation of phosphate calculi *

Corcoran *et al.*[152] conclude from 5 patients with chronic pyelonephritis and hypertension that the pattern of disturbed renal function is nearly identical with that present in their group called established essential hypertension. In patients in whom the inflammatory reaction was acutely active at the time of study the

* The role of infection in the formation of phosphate and calcium calculi is somewhat confused The Michies, in unpublished observations in the writer's laboratory, found that urine collected from the pelvis may be acid when the

[illegible] alkaline in consequence of ureolysis Moreover, B coli commonly ferments glucose to form acetic acid but certain strains obtained from patients with pyelitis prefer to split urea to form ammonia and other strains can be selectively cultured to do this Any statement about the type of infection, the reaction of the urine, and the formation of stones is therefore difficult.

filtration rate and filtration fraction were greatly reduced and RBF/Tm_D increased.

Raaschou[1665] has reported on 31 patients with chronic pyelonephritis in all stages of the disease. His earlier observations were made with a single intravenous injection of inulin and diodrast, but later he recognized the errors inherent in this technique and his interpretations are duly qualified with respect to these errors. He found that clinically the condition of the patient remained good until the inulin clearance fell below 30 cc. (23 per cent of normal) or Tm_D fell to 7 mg. of iodine (17 per cent of normal). Even in advanced stages, the patient may preserve tolerable or excellent health despite greatly reduced renal function. As noted above, the histological preservation of the glomeruli is not a reliable sign of function; patients may die in uremia with completely normal-appearing glomeruli. Whether the uremia stems from obstruction of the tubules or from reabsorption of glomerular filtrate is undetermined, but in the light of the total picture—preservation of the glomerular structure with atrophy and dilatation of the proximal tubules—it would seem that the latter probably plays an important role.

The urea/inulin clearance ratio preserved in the mean its normal range, but the data are not analyzed in terms of inulin U/P ratio.* As is to be expected, the blood urea does not rise above that indefinite ceiling called 'normal' (Raaschou uses 50 mg/100 cc.) until the inulin clearance is reduced to more than one-quarter of the normal value.

Tm_D varied in Raaschou's patients from normal values down to practically zero. He conceives that interstitial fibrosis with invasion of the parenchyma not only leads to the formation of impotent nephrons but decreases diffusion between the capillary plexus and functional tissue, while occlusion by casts obstructs tubules and collecting ducts. Indicative of impotent nephrons is

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the fact that the C_{IN}/Tm_D ratio is generally high, ranging from the normal mean value of 2.6 up to values of 4.5 or even higher. Excluding increased filtration, which is improbable, the only alternative explanation is reduction of excretory power in the tubule. This result is consonant with the preservation of glomeruli and atrophy of tubules in and near scarred areas.

The diodrast clearance in Raaschou's series also ranged from normal down to very low values With this reduction, the C_D/Tm_D ratio remained in the low normal range of 8 to 14 (normal 14 ± 2 16), from which he concludes that the diodrast clearance is reduced because Tm_D is reduced. The filtration fraction, either as related to C_D/Tm_D or to C_D, is normal to high, a fact which he relates to reduction in tubular clearance as revealed by the reduction in C_D and Tm_D. There seems to be a contradiction of interpretations here. The data clearly indicate the existence of impotent nephrons, because of the excessively high values of C_{IN}/Tm_D Accepting this fact, the blood from the glomeruli of such impotent nephrons should be, in part at least, available for clearance by residual functional tissue, leading to vicarious hyperemia of this tissue or a high C_D/Tm_D ratio In view of the fact that this ratio is characteristically on the low side of normal (indeed it is rarely above the normal male figure of 14 and falls as low as 6.69 with a Tm_D of 9.66 mg. of iodine), some circumstance must be operating to reduce renal blood flow to the renal parenchyma as a whole, and particularly to residual functional tissue, apart from glomerular obliteration One obvious possibility is that passive compression of the kidney, issuing from perinephritic contraction of the capsule, supplemented by the formation of scar tissue within the kidney, increases intrarenal pressure, as a result of which the residual functional tissue has less blood available to it for clearance than it would otherwise have. A second possibility is that some tubules are marginally situated with respect to perfusion, they would be measured in long-continued saturation studies and thus contribute to the maximal value of Tm_D, but might not be reached in short-period clearance studies The explanation of the high filtration fraction is perhaps complicated. The most obvious explanation is that postglomerular blood escapes from the kidney without being exposed to tubular excretory tissue, leading to a

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The diodrast clearance in Raaschou's series also ranged from normal down to very low values. With this reduction, the C_D/Tm_D ratio remained in the low normal range of 8 to 14 (normal 14 ± 2.16), from which he concludes that the diodrast clearance is reduced because Tm_D is reduced. The filtration fraction, either as related to C_D/Tm_D or to C_D, is normal to high, a fact which he relates to reduction in tubular clearance as revealed by the reduction in C_D and Tm_D There seems to be a contradiction of interpretations here. The data clearly indicate the existence of impotent nephrons, because of the excessively high values of C_{IN}/Tm_D. Accepting this fact, the blood from the glomeruli of such impotent nephrons should be, in part at least, available for clearance by residual functional tissue, leading to vicarious hyperemia of this tissue or a high C_D/Tm_D ratio. In view of the fact that this ratio is characteristically on the low side of normal (indeed it is rarely above the normal male figure of 14 and falls as low as 6 69 with a Tm_D of 9 66 mg. of iodine), some circumstance must be operating to reduce renal blood flow to the renal parenchyma as a whole, and particularly to residual functional tissue, apart from glomerular obliteration One obvious possibility is that passive compression of the kidney, issuing from perinephritic contraction of the capsule, supplemented by the formation of scar tissue within the kidney, increases intrarenal pressure, as a result of which the residual functional tissue has less blood available to it for clearance than it would otherwise have A second possibility is that some tubules are marginally situated with respect to perfusion; they would be measured in long-continued saturation studies and thus contribute to the maximal value of Tm_D, but might not be reached in short-period clearance studies The explanation of the high filtration fraction is perhaps complicated The most obvious explanation is that postglomerular blood escapes from the kidney without being exposed to tubular excretory tissue, leading to a

filtration rate and filtration fraction were greatly reduced and RBF/Tm_D increased.

Raaschou[1865] has reported on 31 patients with chronic pyelonephritis in all stages of the disease. His earlier observations were made with a single intravenous injection of inulin and diodrast, but later he recognized the errors inherent in this technique and his interpretations are duly qualified with respect to these errors. He found that clinically the condition of the patient remained good until the inulin clearance fell below 30 cc. (23 per cent of normal) or Tm_D fell to 7 mg. of iodine (17 per cent of normal). Even in advanced stages, the patient may preserve tolerable or excellent health despite greatly reduced renal function. As noted above, *the histological preservation of the glomeruli is not* a reliable sign of function; patients may die in uremia with completely normal-appearing glomeruli. Whether the uremia stems from obstruction of the tubules or from reabsorption of glomerular filtrate is undetermined, but in the light of the total picture—preservation of the glomerular structure with atrophy and dilatation of the proximal tubules—it would seem that the latter probably plays an important role.

The urea/inulin clearance ratio preserved in the mean its normal range, but the data are not analyzed in terms of inulin U/P ratio.* As is to be expected, the blood urea does not rise above that indefinite ceiling called 'normal' (Raaschou uses 50 mg/100 cc.) until the inulin clearance is reduced to more than one-quarter of the normal value.

Tm_D varied in Raaschou's patients from normal values down to practically zero. He conceives that interstitial fibrosis with invasion of the parenchyma not only leads to the formation of impotent nephrons but decreases diffusion between the capillary plexus and functional tissue, while occlusion by casts obstructs tubules and collecting ducts. Indicative of impotent nephrons is

* In 4 patients the urea/inulin clearance ratio exceeded 1.0, rising to values as high as 1 5 or more. In 2 instances (examinations 6 and 26) the protocols leave one in doubt about technical errors, but in the other 2 (examinations 12 and 46) the protocols do not indicate a source of error so large and suggest that the phenomenon is real. Raaschou discusses sources of error, and suggests that inulin may fail to penetrate the damaged glomerular membranes or urea may be excreted by the tubules He seems to favor the first interpretation.

the fact that the C_{IN}/Tm_D ratio is generally high, ranging from the normal mean value of 2.6 up to values of 4.5 or even higher. Excluding increased filtration, which is improbable, the only alternative explanation is reduction of excretory power in the tubule. This result is consonant with the preservation of glomeruli and atrophy of tubules in and near scarred areas.

The diodrast clearance in Raaschou's series also ranged from normal down to very low values. With this reduction, the C_D/Tm_D ratio remained in the low normal range of 8 to 14 (normal 14 ± 2.16), from which he concludes that the diodrast clearance is reduced because Tm_D is reduced. The filtration fraction, either as related to C_D/Tm_D or to C_D, is normal to high, a fact which he relates to reduction in tubular clearance as revealed by the reduction in C_D and Tm_D. There seems to be a contradiction of interpretations here. The data clearly indicate the existence of impotent nephrons, because of the excessively high values of C_{IN}/Tm_D. Accepting this fact, the blood from the glomeruli of such impotent nephrons should be, in part at least, available for clearance by residual functional tissue, leading to vicarious hyperemia of this tissue or a high C_D/Tm_D ratio. In view of the fact that this ratio is characteristically on the low side of normal (indeed it is rarely above the normal male figure of 14 and falls as low as 6.69 with a Tm_D of 9.66 mg. of iodine), some circumstance must be operating to reduce renal blood flow to the renal parenchyma as a whole, and particularly to residual functional tissue, apart from glomerular obliteration. One obvious possibility is that passive compression of the kidney, issuing from perinephritic contraction of the capsule, supplemented by the formation of scar tissue within the kidney, increases intrarenal pressure, as a result of which the residual functional tissue has less blood available to it for clearance than it would otherwise have. A second possibility is that some tubules are marginally situated with respect to perfusion, they would be measured in long-continued saturation studies and thus contribute to the maximal value of Tm_D, but might not be reached in short-period clearance studies. The explanation of the high filtration fraction is perhaps complicated. The most obvious explanation is that postglomerular blood escapes from the kidney without being exposed to tubular excretory tissue, leading to a

reduction in E_{PAH} and hence in C_D (in one-half of Raaschou's patients C_D is less than 300 cc/min.). Perhaps this is what the author means when he says that C_D must be reduced because Tm_D is reduced. Cargill [328] has reported E_{PAH} as 0.75 and 0.73 in 2 patients with pyelonephritis whose PAH clearances were, respectively, 206 and 83 cc., and whose inulin clearances were 50 and 20 cc. Compensatory dilatation of the afferent arterioles might contribute to increased filtration rate, while increased intrarenal pressure operating upon the peritubular capillaries might raise the glomerular pressure; in this instance, unlike the normal kidney, this increased intrarenal pressure might not operate to oppose the filtration process itself because of the protection afforded by the periglomerular fibrotic capsule.

Whatever the interpretation, changes in renal function in pyelo*nephritis differ from those in essential hypertension and chronic* glomerulonephritis

In essential hypertension, increased arteriolar tonus reduces the renal plasma flow; the filtration rate is well maintained until arteriolar lesions obliterate the glomeruli, while Tm_D decreases early, ahead of the filtration rate, and therefore C_D/Tm_D tends to be decreased and the filtration fraction increased.*

In glomerulonephritis, the glomeruli are primarily affected; hence the filtration rate is decreased, while the renal plasma flow and Tm_D tend to be maintained, leading to a low filtration fraction and low C_{IN}/Tm_D ratio.

In pyelonephritis, tubular injury outruns glomerular injury, and what we suppose to be contraction of the kidney with increased intrarenal pressure reduces perfusion; hence the renal plasma flow and Tm_D are decreased, the ratio C_D/Tm_D remaining in the normal range. Glomerular injury being late in the sequence, the filtration fraction and the C_{IN}/Tm_D ratio tend to be increased.

* Raaschou, in commenting on the high filtration fraction in *essential hypertension*, notes that an increase in this fraction may in part be due to *impairment of tubular excretion* (reduction of E_D) and implies (pp. 157 and 160) that this possibility was overlooked by Goldring, Chasis, Ranges, and Smith [178] On the contrary, these authors separated their subjects into *those with* impotent nephrons as indicated by high C_{IN}/Tm_D *ratios (group A) and those with normal* ratios (group B), and based their conclusions with *regard* to increased arteriolar tonus solely upon this *differentiation*

The quantitative xanthoproteic reaction,* which reveals the presence in serum of various aromatic metabolic products which are possibly normally excreted by the tubules, increases rapidly as Tm_D is reduced, but shows wide variability at low values of Tm_D. The alkali reserve remains above 55 cc. of carbon dioxide per 100 cc. of blood until Tm_D is reduced below 10 mg., and hemoglobin does not in general fall below 80 per cent until Tm_D reaches this value.

The author speaks of the plasma concentration of diodrast at which the clearance is first depressed because of saturation of some nephric units at the self-depression limit. This figure, he finds, normally lies between 5 and 12 mg of iodine per 100 cc., most frequently between 10 and 11 mg., Tm_D being reached (saturation limit) between 6 and 13 mg of iodine per 100 cc. The accuracy of determination of either limit is not great unless very careful titration experiments are carried out, but Raaschou believes that in pyelonephritis the self-depression limit lies within the normal margins; in a few cases it was higher than normal, but never less than normal. Although it is doubtful if his data are sufficiently detailed and quantitative to warrant a confident conclusion, he believes that tubular excretion in the course of disease follows an all-or-nothing law; the residual functional tissue saturates at the same plasma level as normally. This would imply no vicarious hyperemia, a conclusion difficult to accept in view of the existence of impotent nephrons as indicated by his high C_{IN}/Tm_D ratios † The writer believes that a more detailed titration is required to answer this question.

One phenomenon of some interest recorded by Raaschou is that, in some patients with greatly reduced renal function, Tm_D in consecutive clearance periods tends to increase despite the maintenance of an adequate and more or less constant plasma level of iodrast. He notes that this rising Tm_D was not observed by him normal subjects, and has not been recorded by others in studies the diseased kidney. He discusses and, at least in certain in-

*This reaction is increased in the terminal phase of all progressive bilateral al disease

The normal frequency distribution curve given in figure 51 of Raaschou's r is apparently miscalculated, having its lower origin at 0 1 instead of 0 6 e T/Tm begins to drop below load/Tm

*stances, dismisses the possibility of error from dead space or er*roneous inulin clearance and the possibility of increasing intrinsic tubular activity. He notes but reaches *no final opinion on the possibility* that considerable time may be required for diodrast, either by diffusion or circulation of interstitial fluid, to reach certain tubules which have become isolated by poorly vascularized connective tissue.

The writer has examined the protocols of Goldring, Chasis, Ranges, and Smith[798] on Tm_D in 60 patients with essential hypertension, in all of whom 5 consecutive periods were collected for this measurement. He finds that Tm_D showed a tendency to increase in only 2 out of 91 instances. Assuming that the phenomenon in pyelonephritis is a valid one not attributable to technical error, it appears to be present in this disease (in certain instances only) and not in hypertension or nephritis.*

POLYCYSTIC DISEASE

Polycystic disease of the kidney is a congenital disease which may manifest itself either in the newborn, in which case it is usually quickly fatal, or as an affliction of adult life, when it is compatible with a long period of survival. Lambert,[1193, 1196] who reviews the literature, has made graphic reconstructions of nephrons from two

* The writer would like to suggest that the last explanation proposed by *Raaschou be considered seriously;* the pathological changes in pyelonephritis are such as to lead to severe restriction of the circulation of both blood and interstitial fluid, and this impairment may leave many functional tubules with a [illegible] to occur in nephritis or hypertension, to judge from the pathology of these diseases Indeed, the titration of hypertensive patients indicates that tubular perfusion is well maintained long after arteriolar lesions have markedly im- [illegible] nctional [illegible] of tubu- [illegible] tration [illegible] y vicar- [illegible] question [illegible] ortance [illegible] exami- [illegible] tion at [illegible] successive constant plasma levels each of which is maintained for a considerable period of time

polycystic kidneys in the newborn and confirms the view that th cystic nephrons are always separated from their collecting duct and exist as closed vesicles But formation is not necessarily a re sult of failure of fusion of the tubules and collecting ducts, for it may be that cyst formation in early fetal life is itself the cause of the dissociation between the two embryonic elements.

Graphic reconstructions of 5 cases of polycystic disease of the adult showed that glomerular cysts were closed cavities, but it is demonstrated that cysts appearing along the course of the tubules are, as far as can be determined, connected with the collecting ducts and the renal pelvis Lambert believes that they develop independently of such factors as failure of the tubule to unite with a collecting duct, incomplete development of the tubule, or occlusion of the collecting ducts. The reason for their development remains unknown

In 2 adult patients, 30 to 40 gm of inulin were injected into the peritoneal cavity shortly before death. Puncture of the cysts in both kidneys in one patient made possible removal of 4 samples of cystic fluid before injection of inulin. These samples contained no significant inulinoid blank. The kidneys of both patients were removed immediately after death, and inulin was found in the fluid of most of the cysts in amounts ranging from 10 to 35 mg/100 cc. (the plasma contained 80 to 100 mg/100 cc.), demonstrating the persistence of glomerular function. In 3 cysts the hydrostatic pressure ranged from 10 to 14 mm. Hg, pressures well below the filtration pressure and about equal to the intrarenal pressure.

The endogenous creatinine and urea concentrations of the cystic fluid were in some instances many times higher than that of the blood, indicating that water was absorbed by the cystic nephrons. The urea U/P ratio was generally lower than that of creatinine, indicating that urea was returned to the blood by tubular reabsorption. In a few samples urea and creatinine concentrations in the cysts were equal to those of the blood samples collected the day before death, but the U/P ratios varied with the location of the cyst in the nephron and were lowest and near 1.0 in glomerular cysts and highest in the more distally located cysts The relationships of the urea, chloride, and endogenous creatinine U/P ratios were much as is observed in the bladder urine.

A mixture of trypan blue and India ink was injected into a cyst by renal puncture 24 hr. before death of one of the patients. Sections showed that trypan blue had been taken up in the cells of the tubule proximal to the cyst, while India ink had been taken up only in the distal part of the proximal tubule. This is the only demonstration on record of the absorption of a particulate colloid by the human nephron.

PTOSIS AND UNILATERAL RENAL DISEASE

In one subject examined by Chasis and Redish[160] in whom the right kidney dropped when an erect position was assumed, the ureteropelvic junction remained fixed, thereby producing an acute angulation of the ureter. Unilateral study revealed that with this ptosis the renal plasma flow decreased from 225 to 110 cc/min., although it remained unchanged in the left kidney (208 and 193 cc/min., respectively). In other cases of ptosis examined by them there was no functional disparity in the supine position.

Chasis and Redish emphasize that many common variations in ureteropyelograms are without physiological significance. Pyelographic abnormalities are not necessarily associated with functional disparity and, conversely, marked functional disparity may not be associated with pyelographic abnormalities.

They also note that urine is usually formed at about the same rate in the two normal kidneys in dog and man, but over short periods of time there may be marked differences in the rate of discharge from the pelvis through ureteral catheters. This is not wholly a matter of pelvic discharge, for there may actually be differences in water reabsorption as shown by U/P ratios, and in such cases the concentration of test substances (phenol red, diodrast, etc.) in the urine will also vary inversely as the urine flow and may lead to misinterpretation of the results of renal excretory tests. McCann and Romansky's[1310] study of nephroptosis has been cited in chapter XXIII.

RENAL DIABETES

In occasional otherwise normal individuals glucose may be present in the urine at normal or slightly elevated plasma glucose levels[189] Although the filtration rate and renal plasma flow are generally

normal, Tm_G has been found by most investigators to be reduced.[333,715,827,1527,1849,1998,2102] Certainly, in many subjects the condition represents glomerular-tubular imbalance, as defined by an anomalous spread to the right in the frequency distribution curve of glomerular activity, c_{in}/tm_g.[1931,1939] In some subjects in whom glucose Tm is below the normal range there is some reduction in Tm_D [333] but no reduction in the capacity to reabsorb phosphate.[827] More extended studies of tubular activity will be necessary before it can be said to what extent the lesion is specific.

HYDRONEPHROSIS

Hydronephrosis follows obstruction of the free flow of urine from the kidney. Whereas complete obstruction of the excretory ducts of other glands (salivary, pancreatic, biliary) leads to primary atrophy and necrosis, primary atrophy of the kidney rarely follows even complete obstruction of the ureter except when anuria is initially present. Partial ureteral block invariably leads to hydronephrosis, while only occasionally will complete block lead to primary atrophy.[1009]

In man, early hydronephrosis is characterized by an edematous, hemorrhagic kidney with mushy papillae and easily ruptured pelvic epithelium. The collecting tubules are dilated, with less frequent dilatation higher in the nephron. The tubular epithelium is atrophic and flat and is ultimately replaced by interstitial fibrosis. The glomeruli are less affected and normal-appearing glomeruli may be present in the center of destroyed or cystic tubules. The effect on the blood vessels is variable. The interlobar and arcuate vessels are compressed, but many interlobular arteries still function to supply glomeruli and associated tubules. The hydronephrotic injury works from the fornices to the periphery.

Hinman[1011] notes that the structural changes in experimental hydronephrosis differ in various species, and that such changes cannot confidently be transposed to the human kidney. He finds that when the ureter is tied in the rabbit the renal pelvic contents gradually increase up to 50 to 60 cc. and then decrease. If phenol red is placed in the ligated ureter, the dye completely disappears in 48 hr., indicating that the hydronephrotic sac is not a stagnant pool. He likens it to a fresh-water lake with constant circulation of

fluid. The problem is, how does the urine escape from an obstructed pelvic cavity.

PYELOVENOUS BACKFLOW

It is well known to urologists that the use of moderate to excessive pressure during the injection of contrast medium into the ureter for retrograde pyelography is sometimes accompanied by penetration of the medium into the renal venous tree, the lymphatics, or the subcapsular space, as revealed by x-ray. The mechanism of escape is not yet clearly determined. Hinman and Lee-Brown,[1013] from experiments on sheep, rabbits, and dogs, noted that as the intrapelvic pressure is increased a point of give (30 to 60 mm. Hg) was suddenly experienced, the pressure necessary to maintain backflow thereafter being reduced. Backflow would occur, however, if a pressure of 20 mm. Hg were maintained for a long period. They believed that there was some point of actual communication between the renal pelvis and the large, superficial renal veins in the minor calyces at the base of one or more pyramids, and that through this communication the contrast medium flooded into and completely filled the venous system without extravasation.

Hinman and Lee-Brown developed a theory of hydronephrosis on the premise that, after complete ureteral obstruction, 'pyelovenous' backflow permitted urine to escape from the pelvis into the renal veins, thus accounting for the fact that such a kidney did not undergo atrophy as is the case with secretory glands It was also suggested that, once pyelovenous backflow was established, blood might enter the pelvis from the venous system, accounting for the hematuria in hydronephrosis.

Narath[1500a] has reviewed the anatomy of the fornices and calyces with reference to the propulsion of urine into the pelvis, and arrives at contrary interpretations. Using a modification of Mallory's stain which stains the connective tissue blue and muscle tissue red, he describes the musculature of the calyx. The first muscle encountered in the upper part of the fornix is a longitudinal one extending from the fornix deeply into the parenchyma (*musculus levator fornicis*). Contraction of this muscle has a pulling effect on the fornix. At the neck of the calyx and extending the papilla is the *sphincter papillae*, first described by Henle. Since

the action of this muscle is to close the neck of the calyx against the space below the fornix around the papilla, Narath calls it the *musculus sphincter fornicis*, rather than the *sphincter papillae*. In the wall of the calyx, extending from the sphincter to the pelvico-calyx junction, are longitudinal fibers comprising the *musculus longitudinalis calycis*, whose function is in part to shorten the length of the neck. In the wall of the pelvis and separating the calyx from it is the *musculus sphincter calycis* whose fibers are crossed by part of the above *longitudinalis* muscle.

There are two phases in the motion of the calyx, a collecting and an emptying phase During the collecting phase the *levator fornicis* is relaxed and the fornix sinks downward. As the *sphincter fornicis* relaxes, the upper part of the *longitudinalis* contracts and the calyx assumes the shape of a goblet in which the urine accumulates. Backflow of urine from the pelvis into the calyx is prevented by closure of the *sphincter calycis* He believes that the formation of this goblet creates a negative pressure which acts to drain urine from the canaliculi of the papilla

In the emptying phase, the *sphincter calycis* opens and urine flows into the pelvis The *sphincter fornicis* closes and the upper part of the *longitudinalis* relaxes to form a cap against the papilla. The contraction of the *levator fornicis* pulls this cap tight and prevents backflow into the canaliculi and the tubular system. Simultaneously the lower part of the *longitudinalis* contracts, assisting the relaxation of the *sphincter calycis* and reversing the process of goblet formation. The sphincter of the ureteropelvic junction opens when the *sphincter calycis* is closed and closes when *sphincter calycis* is relaxed

The description above is based upon the movements of the alyces as observed in normal individuals in whom a catheter had en introduced between 6 and 12 cm up the ureter, the renal lvis filled with radio-opaque solution and observed either with nagnifying glass or by rapid photography

When outflow from the catheter was blocked, the patient soon erienced renal colic due to the increase in renal pelvic pressure. his time serial pictures indicated that the routes of the retro- e injection were:

1. Pyelocanalicular backflow. This is revealed by a characteristic brush-like extension of contrast medium for a short distance into the canaliculi. The ultimate destiny of the contrast medium was not determined; it might return to the pelvis when the pressure was released, or it might be absorbed by the tubules or lymphatics.

2. Pyelosinus transflow. This represents a flow of contrast medium from the calyx into the renal sinus. It can occur with very little intrapelvic pressure or under such pressure as to rupture the fornix. In the former instance, Narath believes the contrast medium is absorbed by the fornices to enter the lymphatics. It takes variety of shapes—hornshaped, multiform, plane-like, and ribbon-like—but that its ultimate destiny is lymphatic absorption is demonstrated by clear visualization of the medium leaving the *renal sinus by lymphatics and draining into adjacent lymph nodes.*

3. Sinovenous ingression. Narath believes this occurs only when the fornix actually ruptures. Frequently when this occurs the interlobar and arcuate veins are outlined, which helps to distinguish it from pyelosinus transflow. The ultimate destination of the dye is again lymphatic absorption.

Narath believes that Hinman's terms 'pyelovenous backflow' have been used too loosely to describe every type of extravasation, and he would restrict them to the traumatic production of sinovenous ingression.

The role of traumatic injury in 'pyelovenous backflow' has also been emphasized by Rolnick and Singer [1741] They repeated some of Hinman's injection experiments in dogs and found that actual tears could take place at pressures varying from 23 to 150 mm. Hg. These tears were at the pelvic poles and varied in size with the force employed. Low pressures produced small tears in the calyces and the contrast medium then passed into the lymphatics or veins.

Druckmann and Schorr [545] described 3 cases of rupture of the kidney pelvis during retrograde pyelography (contrast medium not named). All 3 patients had diseased kidneys and 1 had severe necrosis of the pelvis. The x-ray film presented a smooth, sharp, convex lower border of contrast medium conforming with the capsule, which is what would be expected from perforation into

the subcapsular space. When this complication occurred all patients complained of severe pain, chills, and fever, and 1 patient died.

Such x-ray pictures indicate the consequences of gross rupture of the pelvis, but a minute rupture of the calyx sufficient to produce 'pyelovenous backflow' undoubtedly presents a different picture.

The development of hydronephrosis in the rat when the ureter is completely occluded is not accelerated by forced water, saline, or urea diuresis, or retarded by water deprivation [1012]

Levy, Mason, Harrison, and Blalock,[1233] using the venous sound method, found that the renal blood flow and oxygen consumption were reduced by total ureteral obstruction, but the lowest values reached a day or so prior to death were usually above 50 per cent of the control value. Maximally increased intrarenal pressure (if this is the sole factor operating) can substantially reduce but not completely occlude the renal circulation

OTHER RENAL DEFECTS

Among congenital or acquired renal defects may be mentioned the de Toni-Fanconi syndrome (rickets, acidosis, hypophosphotemia, renal glycosuria),[1242a] vitamin D-deficiency rickets,[923] and the Butler-Albright syndrome [612, 1223] In the last-named syndrome a lesion, chiefly of the distal tubule, leads to deficient acidification of the urine, deficient ammonia formation, excessive reabsorption of chloride and depletion of plasma bicarbonate (chloride acidosis) accompanied by polyuria and low specific gravity (1.010 or less), insensitivity to ADH, phosphate depletion, retarded growth, rickets, and nephrocalcinosis. Faber, Abramson, and Silverberg in the *Festschrift for Thomas Addis* [612] suggest that the primary fault is attributable to a deficiency of carbonic anhydrase in the distal tubule cells A related instance of inability to conserve bicarbonate is described by Stapleton [1979]

TEMPORARY INHIBITION OF FUNCTION

nnelly [588] reports 4 subjects, referred for routine intravenous lography, who on first examination showed absence of function on one side. On repetition of the examination 48 hr. later,

both sides showed normal function. There was no evidence of calculus formation and the minor calyces, when visualized at the second examination, were normal.

It is the writer's impression that this experience is not uncommon among urologists, although it is rarely reported. It is probably generally true that failure of visualization of a kidney after intravenous pyelography may be traced to obstruction of the ureter by a calculus which is subsequently passed, to ureteral spasm, to previous retrograde pyelography with sodium iodide or other irritating solutions, or other urologic causes. In every case these should be excluded before drawing the conclusion either that a functional kidney is absent or that functional inhibition of urine formation has occurred.

That true functional inhibition occurs in a subject with an essentially normal kidney on both sides (i.e. apart from obstruction or other urologic fault) is rendered doubtful by the large number of observations now available on renal plasma flow and Tm_D or Tm_{PAH}. Admittedly, not many of these patients have been examined a second time, but many of them would have been had they been selected on the basis of giving no history of renal disease, and then found to have total renal function only half of normal.

WHEN IS THE KIDNEY NOT A KIDNEY?

The eminent pathologist, Jean Oliver, is among those who attribute to clearance methods disabling ambiguity. Since over some years he has continued refractory in this position, on the principle that 'if you can't lick 'em join 'em,' we should like to quote with enthusiasm form his illuminating essay 'When is the Kidney not a Kidney?': [1553]

'The answer I would give to [this] question is therefore now apparent. There is no "kidney," either structural or functional, in chronic renal disease. The only useful or meaningful purpose of the word that possibly remains under these conditions is to designate a mass of tissue which, except in topographical anatomic or surgical problems, has no significance until we analyze its constituents. And then it vanishes into the disparity of thousands of fantastically altered organs of strange design and anomalous behavior.

'A semantist who might have followed my discourse thus far with considerable impatience, would at this point doubtless interrupt with the suggestion that our difficulty can be easily solved He would point out that on the unnamed Objective Level of the Structural Differential are the nephrons, normal or abnormal, and that all we need to do to be consistent and clear is to call them by their right names on the Descriptive Level. Liquidate the "kidney" and entitle the next symposium "The Nephrons in Health and Disease"

'Such forthrightness may be a simple procedure for a young and vigorously growing scientific discipline that makes its own terms with its problems. But we in medicine have an ancient and proud tradition that binds us with chains which we are loathe to shed since their bond is to the great men and ideas of our past Thus we continue to use as symbols of that past conceptual terms that have lost all but their honorary content. What, for example, is the present significance of Virchow's "degeneration," by which is still designated a whole category of disease, including one that has here concerned us?

'And so we shall doubtless continue to talk of the "kidney" of chronic renal disease and of Bright's disease But while we are talking, there is no reason why we should not also be thinking and in the interior realm of the idea we can discriminate the Kidney in Health, if you will, but the Nephrons in Disease'

CHAPTER XXVII

Diuretics

The term 'diuretic' has generally been used to describe any agent which will produce an increased excretion of urine, a usage which is ambiguous. In a multitude of circumstances, oliguria persists because of renal ischemia associated with circulatory insufficiency; any therapy which restores the circulation to an adequate level may be expected to increase urine production, in the absence of persistent renal injury, by improving renal blood flow and glomerular activity.

It has frequently been suggested that some diuretics act by altering the 'water binding' power of the plasma proteins, or by causing a shift of electrolytes and water between tissues and plasma, but the evidence for such modes of action is meager and their possible contribution to the action of known diuretics may be set aside as unproved. We shall confine the term diuretic to substances that promote the excretion of salt or water by their local action on the kidney.

Increased excretion of water might result from interference with the formation of ADH in the neurohypophysis, with its secretion, or with its action on the renal tubule. These possibilities are unfulfilled clinically or experimentally except in clinical or experimental diabetes insipidus. A pharmacological method of producing diabetes insipidus remains to be discovered. Some

clinical cases of diabetes insipidus have been interpreted as due to insensitivity of the renal tubules to ADH, while the polyuria which frequently follows protracted renal ischemia (shock, etc.) or chemical injury (carbon tetrachloride poisoning, etc.) as well as the clinical state of hyposthenuria, may be referable to specific tubular injury, but what segment of the tubule is affected is unknown. More commonly, an increased excretion of water may be the result of decreased proximal reabsorption of some solute (glucose in phlorizinized animals) in consequence of which the load of water delivered to the distal system exceeds its reabsorptive capacity. Or the agent may block the proximal or distal reabsorption of sodium, and (directly) by increasing the distal load of water or (indirectly) by hemodilution lead to increased water excretion. The first is the mechanism of osmotic diuresis as observed experimentally after the administration of hypertonic sodium chloride solutions or of such substances as sucrose, mannitol, and urea, and clinically in diabetes mellitus where glucosuria reduces proximal water reabsorption.

OSMOTIC DIURESIS

The intricate problems of glomerular-tubular balance, the conditions of proximal reabsorption, and the possible limitations in distal reabsorption of sodium chloride and water have been discussed in chapter XI It will suffice to say in summary that any urinary solute, if excreted at a sufficient rate, will retard the proximal and possibly the distal reabsorption of water and accelerate the urine flow. Although the expression 'osmotic diuresis' is misleading, because it is not the osmotic pressure of the final urine that is the critical factor in producing diuresis but the osmotic resistance offered to the passive reabsorption of water in the proximal tubule and thin limb, it would seem advisable to retain it for the time being The substances most frequently used to induce osmotic diuresis are urea, sucrose, mannitol, sodium sulphate, and hypertonic sodium chloride solutions Mannitol and sucrose are useful as osmotic diuretics in relieving the edema of the nephrotic syndrome but, as pointed out in chapter XXIV in the discussion of anuria, there is no evidence that osmotic diuretics are or can be useful in anuria or oliguria associated with renal failure; at best

they force the excretion of water in the residual functional nephrons without significantly promoting the excretion of metabolites or restoring electrolyte and water balance, and there is rarely any physiological warrant for their use. In the absence of a route for excretion, they present a real danger.

Acidifying salts such as ammonium chloride, ammonium thiosulphate, and calcium chloride apparently act in the ultimate as osmotic diuretics; the distal secretion of ammonia entails water for the excretion of whatever ammonium salts may be present in the urine. Whether the secretion of ammonia into the distal tubule urine influences the distal reabsorption of sodium is not determined.

MERCURIAL DIURETICS

Mercurophylline (*mercuzanthin*, *mercupurin*)
Meralluride sodium (*mercurhydrin*)
Mersalyl-theophylline (*salyrgan*, *merthyl*)
Thiomerin
Neptal

All soluble mercury compounds in doses insufficient to produce necrosis accelerate the excretion of sodium and to a lesser extent of water. Among organic derivatives, which are selected for low toxicity and high natriuretic power, some are more potent than others, the diuretic activity apparently being correlated with differences in the solubility of the salts.[651] It has generally been accepted that the action of organic mercurial compounds is attributable to their ionization and liberation of mercuric ions,[1962] but such compounds have a very low degree of ionization and in some instances are equally active, mol for mol of mercury, with inorganic salts in the inhibition of sulfhydryl and other enzyme systems,[820,966] and in the *in vitro* tubular excretion of phenol red (Taggart and Forster, pers. com.). It seems probable, therefore, that their natriuretic action is attributable to the properties of the organic complex as such.

Since mercury, like other heavy metals, is known to block sulf-hydryl groups in enzymes, it might be supposed that this action accounts for its effects on the renal tubules However, organi mercurials form complexes with other (amide and carboxy

groups, and the mechanism of their action in the kidneys is not established. BAL (2,3-dimercaptolpropanol), which forms a poorly dissociable complex with mercury, accelerates its excretion [776] and has been used to good effect in the treatment of mercuric chloride poisoning.[1265] It also prevents or promptly interrupts the diuresis and chloruresis induced in dogs and rabbits by mercupurin and mersalyl.[562, 616, 900] BAL is apparently without effect on the filtration rate or renal plasma flow. It has a marked but transient antidiuretic action in water diuresis, probably by stimulating the secretion of ADH.

It has been suggested that the action of mercurial diuretics is extrarenal, but there is no convincing evidence that diuresis involves any action other than that on the renal tubules. Govaerts [824] has shown that, once diuresis is induced in a kidney by novasurol, perfusion with normal blood does not check it. Mercurials act on the isolated kidney [864] and small doses, if injected into the renal artery of anesthetized dogs, produce diuresis on the injected side and not on the other.[99]

The diuretic action of mercurials is augmented by acidifying salts, particularly ammonium chloride, and, although acidifying salts themselves produce some diuresis, their combination with mercurials may involve a synergistic action [937] Bicarbonate, on the other hand, depresses the natriuretic action of mercurials It has been suggested that both actions are referable to the effects of hydrogen ion concentration of the dissociation of mercuric ions from the organic compound, but in view of the facts cited above this explanation appears to be inadequate If correct, it locates the natriuretic action of mercury at a point coincidental with or distal to the point of acidification of the urine, i e. the distal tubule.

That mercurial diuresis represents an action on the distal system has been argued by Duggan and Pitts [551] on the grounds that the maximal natriuresis obtainable with mercurhydrin in the dog represents about 15 per cent of the filtered sodium load, while superimposition of salyrgan diuresis on pitressin natriuresis increases sodium excretion only to the level attained by salyrgan alone, indicating that both substances act at the same site. In both dog and man,[1638] depression of the filtration rate reduces

dium excretion even during mercurial diuresis, presumably through reducing the distal load by promoting excessive proximal reabsorption.

Dicker [510] has shown that mersalyl (salyrgan) in optimal therapeutic doses in rats increases the inulin clearance about threefold and the diodrast clearance by about 50 per cent. Calomel in one-tenth equivalent dosage of mercury had a similar effect. Thus, in the rat mercurial diuresis involves both an increase in filtration rate and decreased water reabsorption.

But salyrgan does not increase the filtration rate in dogs [131, 471, 726, 1793] or in man,[199, 274, 1563] nor does it affect the renal blood flow in the dog and rabbit in any consistent manner.[2119] In these species, diuresis is solely a result of reduced sodium (and water) reabsorption.

Dicker [510] found that mersalyl (salyrgan) in therapeutic doses reduced Tm_D by about 75 per cent, while calomel had no effect. Brun, Hilden, and Raaschou [274] have shown that mersalyl, when given to man by constant intravenous infusion, impairs the tubular excretion of both Tm_D and Tm_{PAH}, these values being reduced by 60 to 75 per cent. The splay in the diodrast titration curve is greatly widened, so that the diodrast clearance is self-depressed at plasma concentrations only slightly above 1 mg. of iodine per 100 cc., as compared with 5 to 10 mg. of iodine per 100 cc. in the normal subject. After single injections the effect is very rapid and persists for at least 3 hr. Since mersalyl is excreted rapidly, the authors believe that it is excreted by the tubules and that in this process of tubular excretion mercuric ions(?) exert an inhibitory effect on some enzyme in the transport system.

The depression of Tm_{PAH} in man by mersalyl has been confirmed by Berliner, Kennedy, and Hilton,[131] while McDonald and Miller [1315] report that mercuzanthin depresses Tm_{PAH} to some 45 per cent of the control in man, the maximal effect after intravenous injection being reached in 60 min. These investigators find that, after a 2 cc. dose, Tm_G is not depressed, but Weston, Grossman, Edelman, Escher, Leiter, and Hellman [2179] report that 2 cc. doses of mercuzanthin or thiomerin intravenously decreased Tm_G by 40 to 80 per cent, whether the mercurial is given during or before Tm_G measurement. Mercuric chloride, however, does not

produce glucosuria in dogs unless the animals show a 4+ albuminuria and marked renal tubular necrosis. If the contradiction above is resolved in favor of a depressive action on glucose reabsorption, it seems likely that the action is insufficient to decrease Tm_G below the normally filtered load.

Paradoxically, Berliner, Kennedy, and Hilton [131] have demonstrated that neither mersalyl nor small doses of mercuric chloride depress Tm_{PAH} in the dog, despite the fact that in man and dog mersalyl has the same inhibitory effect upon sodium reabsorption. Handley, Telford, and La Forge [904] find that salyrgan and mercurhydrin do not interfere with the tubular transport of PAH or glucose in the dog, as judged by Tm values. The results indicate a significant species difference in the mechanism of tubular excretion in dog and man.

Whether mercurials specifically impede the reabsorption of water itself is undetermined, but the fact that mercurial diuresis does not reduce the osmotic ceiling in the dog (0.3 M sodium chloride), despite an increase in urine flow of 300 per cent,[781] argues against this belief. The obvious effect is upon the reabsorption of sodium (and chloride), the concentration of which in the diuretic urine in the absence of water diuresis is generally such as to suggest that the salt forces water excretion by its osmotic effect.[726] Under any circumstances, the excretion of sodium chloride, by reducing the sodium content of the plasma, releases water for excretion. The immediate quantitative action of various mercurials should therefore be judged in terms of sodium chloride and not water excretion.[1737] Mercupurin apparently has no effect on phosphate excretion.[817] Overdosage leads to reduction in extracellular fluid volume and blood volume and to serious disturbances of the electrolyte pattern of the body fluids, sometimes with mild acidosis, but rarely to mercury poisoning.[809, 1644] However, some mercurial compounds may produce cardiac death in dogs.[1737] The toxicity of mersalyl and meralluride (mercurhydrin) for white rats is diminished by proteinuria induced by human albumin administration prior to mercurial injection, but enhanced if albumin and mercury are given simultaneously.[1248]

Mercurhydrin tagged with $Hg^{203-205}$ when injected intravenously, shows three components in rate of disappearance; the

most rapid component represents mechanical mixing in the blood-vascular system; the second, relatively rapid adsorption on cells or diffusion into remote compartments and tissues; and the slowest component, overall excretion. The rate of urinary excretion of this compound is relatively rapid (half-life about 2 hr.).[2078]

The repeated administration of mercurhydrin, merthyl, and thiomerin intravenously to dogs in doses of 0.39 mg. Hg per kg. per day leads to a reversible reduction of the creatinine clearance by the third day. This reduction is interpreted as a toxic effect, but progressive dehydration of the animal by diuresis is not considered.[902]

It is of interest that salyrgan exerts an anticonvulsant action against procaine, strychnine, picrotoxin, coramin, and metrazol when given intramuscularly to guinea pigs (but not in frogs when the convulsant drugs are injected into the lymph sac). The authors suggest that salyrgan acts, like calcium, to decrease membrane permeability.[135]

The effects of atropine on the diuretic action of mercurials [1210,1211] cannot be resolved without control of the basic variables involved.

XANTHINE DERIVATIVES

Theobromine and theophylline have long enjoyed a vogue as diuretics, especially when coupled with other diuretic measures, despite the absence of any experimental warrant. Caffeine is rarely used clinically. Perhaps it is fair to say that their diuretic action is subtle and, more frequently than not, evasive. Cushny [461] observed that they have a marked diuretic action in the rabbit, a moderate action in man, a very slight action in the dog, and no action in the cat—a statement which may reflect differences only in the circumstances of testing rather than in the species tested. Out of the older literature there emerge only a few facts: that under certain as yet undefinable conditions they tend to increase the filtration rate in the heart-lung-kidney, the perfused kidney, and in anesthetized and unanesthetized dogs and rabbits, but this is not a necessary condition for diuresis, and diuresis when it occurs is not remarkable for its magnitude or duration.[99,199,379,59 726,1512,1563,1712 1793 2110,2139]

The xanthine derivatives are excitatory to the central nervo

system and may modify the secretion of ADH, they have in general a vasodilator action but decrease the cerebral blood flow;[2156] they generally increase cardiac output and improve a poor circulation; they seem to have a direct effect upon the renal circulation, but the qualitative nature of this effect is conditioned to some extent by the *status quo* of the kidneys at the time of their administration (ch. XXII), and they appear to have a specific effect upon sodium reabsorption, but this is probably influenced by glomerular-tubular balance. In view of this multiplicity of action, it would be difficult to defend the position that they cause a shift of electrolytes from tissues to plasma

In chapter XIV, theophylline ethylene diamine and caffeine were discussed under the topic of renal vasodilatation, despite the fact that in the normal subjects studied by Chasis, Ranges, Goldring, and Smith [338] these drugs typically decreased the renal blood flow. The filtration rate was, however, increased In subjects with chronic congestive heart failure, theophylline is reported by Escher and her coworkers [603] to have the same action as in normal subjects except that the initial transient increase in renal plasma flow is longer sustained

Fulton, Van Auken, Parsons, and Davenport,[726] and others before and after them,[1125] showed that xanthine derivatives sometimes increase the excretion of chloride, but Newman [1512] was apparently the first to demonstrate that theophylline specifically inhibits sodium reabsorption in man. This tubular effect has been confirmed by Crutchfield and Wood,[467] Davis and Shock,[477] and Sinclair-Smith, Kattus, Genest, and Newman.[1902] Davis and Shock studied 25 normal subjects before and after the intravenous administration of 0.48 or 0.96 gm of theophylline ethylene diamine. The drug consistently increased the filtration rate, most markedly within the first 10 to 20 min, the maximal increase averaging about 20 per cent. The diodrast clearance generally increased immediately after drug administration to about the same extent, but tended to return to the control level or below. The average filtration fraction remained unchanged immediately after the drug but increased in later periods. The urine flow trebled immediately after injection but gradually returned toward the control level even in those subjects in whom an elevation in fil tion

rate was maintained. The authors emphasize that the sustained diuretic effect is not related to increased sodium excretion but reflects a change in tubular reabsorption of water, because of either direct action on the tubules or changed neurohypophysial activity. Peripheral venous pressure was slightly decreased.

The average sodium clearance increased approximately threefold for 55 to 60 min. after the drug, with no significant change in plasma sodium concentration but with increasing urine sodium concentration in later periods as diuresis regressed.

Sinclair-Smith, Kattus, Genest, and Newman [1902] similarl found that aminophylline (0.24 gm. intravenously) increased sc dium and chloride excretion, without a change in filtration rat in a patient with chronic congestive heart failure in whom cor pensation had been partially effected by digitalis.

Green and his coworkers [848] find that aminophylline and, to a lesser extent, 1,3-diethyl-8-bromoxanthine increase sodium excretion, with only small and variable increases in filtration rate, although they believe that the intensity of the natriuretic effect is proportional to the basal filtration rate; i.e. the higher the initial filtration rate the greater the natriuretic effect.

Theophylline does not interfere with the tubular transport of PAH or glucose in the dog.[904]

Theophylline and aminophylline increase the cardiac output [683, 848, 1042] with little effect upon mean blood pressure. It is important to note that, in reference to renal hemodynamics, it is the mean blood pressure that is important and not cardiac output, which, at a given mean pressure, may have any value without affecting the perfusion of the kidney.

The natriuretic effect of the xanthine derivatives does not appear in any instance to be of sufficient duration to be very useful clinically, and the decreased water reabsorption (possibly effected through central inhibition of ADH secretion) is likewise of insignificant magnitude, even if increased water excretion *per se* (i.e. without sodium) would be physiologically effective in relieving edema.

Formoguanamine has a diuretic and chloruretic effect similar t that of the xanthine derivatives.[1350]

The use of digitalis and the digitalis glucosides in the treatment of chronic congestive heart failure is based primarily upon their action on the heart and venous reservoir. Digoxin is, however, chemically related to the adrenal steroid pattern, and it is of some interest to note evidence of a specific depression of tubular reabsorption of sodium. A preliminary report of Earle, Farber, Alexander, and Eichna (pers. com.)[564] indicates that the intravenous administration of digoxin to 10 patients with congestive failure increased the excretion of water, sodium, and chloride within 15 to 60 min. Sodium excretion increased as much as 0.400 mEq/min. In 5 patients the diuresis was associated with slight increases in filtration rate (60 to 72, 65 to 77, 90 to 100, 75 to 88, and 50 to 67 cc.) but in 5 there was no significant change in this function (41 to 45, 65 to 70, 65 to 64, 92 to 94, and 54 to 54 cc). (In 1 hyponatremic patient [plasma sodium of 114 mEq/liter] an increase in filtration rate from 89 to 112 cc was not accompanied by increased sodium excretion.) In each instance, the diuresis was associated with a fall in venous pressure (brachial or femoral), although in 3 instances the control pressures were in the normal range In 2 patients in whom the measurement was made, the femoral venous pressure declined from 74 to 38 and from 61 to −5 mm water Cardiac output was measured in 5 of these experiments and was increased by digoxin in each However, sodium excretion appeared to increase before any significant change in cardiac output was observed in 4 of the 5 studies

Intravenous digoxin also increased sodium excretion in 5 patients with edema and ascites due to cirrhosis of the liver, and in 2 patients with nephrotic edema, but the absolute increases were considerably less than in patients with congestive failure. In 2 in whom the control rate of sodium excretion was zero, this value after digoxin increased to 0 002 mEq/min. but, in the average, sodium excretion in this group of 7 patients increased from control values of 0.016 to 0.050 mEq/min.

Intravenous digoxin was without natriuretic effect in 5 of 21 normal subjects examined. In 2 subjects there was a questionable increase, while in 14 sodium excretion increased in the average

from 0.028 to 0.114 mEq/min. Renal function was measured in 4 of these and showed no change after digoxin (filtration rate 94 cc. before and 95 cc after digoxin). Femoral venous pressure did not change significantly in the 2 studies during which it was measured (60 to 57 and 130 to 116).

It appears that digoxin may induce diuresis in heart failure by several mechanisms, perhaps the most important being a reduction in renal venous pressure. The drug may cause diuresis without any change in filtration or renal plasma flow and before there is a change in cardiac output The data above suggest that it may also have a direct tubular effect on the reabsorption of sodium, but this effect appears to be too small to be of practical importance.

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